ARCHIVES

OF

THE MIDDLESEX HOSPITAL

VOLUME XIII

Seventh Report

FROM THE

Cancer Research Laboratories

CONTENTS.

London

MACMILLAN AND CO., LIMITED

NEW YORK : THE MACMILLAN COMPANY

JULY 1908

All rights reserved

610.6 Ar2 Jrnl v. 13

Library
of the
Academy of Medicine,
Toronto.
13094

Presented by

Prof. J. J. Mackenzie
1922

ARCHIVES

OF

THE MIDDLESEX HOSPITAL

VOLUME XIII

Seventh Report

FROM THE

Cancer Research Laboratories

EDITED FOR THE CANCER INVESTIGATION COMMITTEE

BY

W. S. LAZARUS-BARLOW, M.D., F.R.C.P.,

DIRECTOR OF THE CANCER RESEARCH LABORATORIES; FOREIGN MEMBER OF THE GERMAN COMMITTEE FOR THE INVESTIGATION OF CANCER; FORMERLY PATHOLOGIST AND LECTURER ON PATHOLOGY AT THE WESTMINSTER HOSPITAL

London

MACMILLAN AND CO., LIMITED

NEW YORK: THE MACMILLAN COMPANY

July 1908

All rights reserved

LIBRARY

JUL 1 9 2002

UNIV. OF TORONTO

Digitized by the Internet Archive
in 2010 with funding from
University of Toronto

http://www.archive.org/details/archives13midd

Cancer Investigation Committee

(1907).

ALFRED PEARCE GOULD, Esq., M.S., F.R.C.S., *Chairman.*
WILLIAM PASTEUR, Esq., M.D., F.R.C.P.
ARTHUR FRANCIS VOELCKER, Esq., M.D., F.R.C.P.
JOHN BLAND SUTTON, Esq., F.R.C.S.
JOHN MURRAY, Esq., F.R.C.S.

Hon. Scientific Secretary.

WALTER SYDNEY LAZARUS-BARLOW, Esq., M.D., F.R.C.P.

Cancer Research Laboratories.

Director.

WALTER SYDNEY LAZARUS-BARLOW, Esq., M.D., F.R.C.P.

Assistants to the Director.

HECTOR ALFRED COLWELL, Esq., M.B.
CECIL WILLIAM ROWNTREE, Esq., M.B., B.S., F.R.C.S.
ARCHIBALD LEITCH, Esq., M.B., Ch.B.

Research Scholars.

Walter Emden Research Scholar:
VICTOR BONNEY, Esq., B.Sc., M.D., M.S., M.R.C.P., F.R.C.S.

Richard Hollins Research Scholar:
LOUIS COURTAULD, Esq., M.A., M.B., B.C.

Medical Officer and Registrar.

ARTHUR FRANK PALMER, Esq., B.A., L.S.A.

NOTICE.

In the following Pages, excepting where an asterisk (*) *is placed, or where the context makes it clear that such is not the case,* EVERY DIAGNOSIS OF MALIGNANT DISEASE HAS BEEN MADE AS THE RESULT OF MICROSCOPIC EXAMINATION.

W. S. L.-B.

REPORTS

FROM THE

CANCER RESEARCH LABORATORIES

TABULATED SYNOPSES OF THE POST-MORTEM EXAMINATIONS AND OPERATIONS IN CASES OF MALIGNANT DISEASE DURING THE YEAR 1907.

By THE DIRECTOR and his ASSISTANTS.

In the following tables are given the results of all cases of malignant disease—as determined by microscopical examination—which were investigated in the Cancer Research Laboratories during the year 1907. The material was derived partly from the post-mortem room and partly from the operating theatre. In all 222 cases (males 64, females 158) of malignant disease have been examined microscopically. All of the above were in-patients. The total number of admissions to the Hospital as in-patients during 1907 was 3,485; viz., 1,671 males, and 1,814 females. In addition, 12 males and 22 females with malignant disease were admitted to the Electrical (Out-patient) Department for X-ray treatment. Histological examination was not made in these cases.

Besides the cases that have been mentioned, a certain number of patients were admitted (either to the general wards or the special wards) in which the diagnosis of malignant disease was not made certain by histological

examination. These are grouped in two classes according to the relative probability of accuracy in the diagnosis.

In the first group the diagnosis was founded on naked-eye appearances or on touch, but the patients were either discharged unrelieved from the Hospital at their own request, or else left relieved after palliative operation (*e.g.*, cases of gastrostomy, colotomy, &c.).

In the second group the diagnosis was made upon clinical grounds alone.

GROUP I.

Cases diagnosed as Malignant Disease on Evidence derived from the Naked-Eye Appearance or by Touch.

Site.	1907.		
	Females.	Males.	Total.
Mouth	—	7	7
Tongue	—	6	6
Jaw	—	1	1
Tonsil	—	1	1
Stomach	3	2	5
Cæcum	3	—	3
Colon	7	—	7
Rectum	7	9	16
Omentum	1	—	1
Breast	29	—	29
Uterus	26	—	26
Vulva	5	—	5
Ovary	2	—	2
Bladder	1	2	3
Testis	—	1	1
Larynx	—	1	1
Rodent Cancer	1	1	2
Skin	—	1	1
Skin (melanotic sarcoma)	—	1	1
Orbit	1	—	1
Eye (melanotic sarcoma)	1	—	1
Bones (sarcoma)	2	1	3
Totals	89	34	123

GROUP II.

Cases diagnosed as Malignant Disease on Clinical Evidence alone.

Site.	1907.		
	Females.	Males.	Total.
Œsophagus	1	6	7
Stomach	1	6	7
Colon	3	1	4
Liver	1	2	3
Pancreas	2	—	2
Abdominal glands	—	1	1
Prostate	—	1	1
Totals	8	17	25

TABLE I.—

	Total.		0—5.		6—10.		11—15.		16—20.		21—25.		26—30.		31—35.		36—40.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
CARCINOMA.																		
Skin ... ... Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Skin ... ... Spheroidal	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Sup. Maxilla ... ... Squamous	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Tongue ... ... Squamous	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Mouth ... ... Squamous	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tonsil ... ... Squamous	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Palate ... ... Squamous	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pharynx ... ... Squamous	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Œsophagus ... ... Squamous	4	1	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—
Œsophagus ... ... Spheroidal	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Stomach, Cardiac end Spheroidal	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
„ Middle ... Columnar	2	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
„ Middle ... Spheroidal	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1
„ Pyloric end Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
„ Pyloric end Spheroidal	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cæcum ... ... Columnar	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Ascending Colon ... Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Sigmoid Flexure ... Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rectum ... ... Columnar	4	4	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Rectum ... ... Spheroidal	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Kidney ... ... Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Bladder ... ... Squamous	1	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Prostate ... ... Spheroidal	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Penis ... ... Squamous	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Cervix uteri ... ... Squamous	—	19	—	—	—	—	—	—	—	—	—	—	—	1	—	2	—	4
Cervix uteri ... ... Spheroidal	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vagina... ... ... Columnar	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vulva ... ... Squamous	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Breast ... ... Spheroidal	—	20	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	2
SARCOMA.																		
Mixed-cell	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Small round cell	3	2	Adrenal.	—	—	—	—	—	—	—	—	Femur.	—	—	—	—	—	—
Myxo-chondro-sarcoma	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	Thigh	—	—
Hæmangeio-sarcoma	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Melanotic	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
ENDOTHELIOMA	—	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2 Cervix uteri.
HISTOLOGY DOUBTFUL	3	7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Cervix uteri.
	38	80																

Post-mortem Cases.

41—45.		46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.		81—85.		86—90.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	2	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	1	—	—	1	—	—	1	1	1	1	—	—	—	—	—	—
—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	1	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—
—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
—	—	—	5	—	3	—	2	—	1	—	—	—	1	—	—	—	—	—	—
—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—
—	3	—	2	—	2	—	3	—	4	—	—	—	2	—	1	—	—	—	—
—	Pharynx.	—	—	—	Pelvis	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	Bladder.	Orbit.	—	—	Lung.	—	—	—	—	—	—	—	—	—	—	Breast
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cervical Glands.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	Skin.	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	Breast	—	—	—	—	—	2 Breast.	—	—	—	—
Larynx Omentum.	Cervix uteri.	Kidney.	Cervix uteri.	—	Omentum.	—	Stomach.	—	Breast	—	—	—	—	—	Peritoneum.	—	—	—	—

TABLE II.—

		Total.		0—5.		6—10.		11—15.		16—20.		21—25.		26—30.		31—35.	
		M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
	CARCINOMA.																
Alimentary Canal.	Lip ... Squamous	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tongue ... Squamous	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Stomach... Spheroidal	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Intestine { Spheroidal	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Intestine { Columnar	1	5	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (colon)
	Generative System { Squamous	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Generative System { Spheroidal	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Generative System { Columnar	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Breast { Spheroidal	—	38	—	—	—	—	—	—	—	—	—	—	—	—	—	3
	Breast { Columnar	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Other Sites { Squamous	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Other Sites { Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	RODENT CANCER	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	SARCOMA.																
	Mixed-cell	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Spindle-cell	2	2	—	—	—	—	—	—	1 (jaw)	—	—	—	—	—	1 (skin)	1 (ilium)
	Round-cell	1	1	1 (scalp)	—	—	—	—	—	—	—	—	—	—	1 (femur)	—	—
	Myeloid	1	—	—	—	—	—	—	—	—	—	—	—	1 (femur)	—	—	—
	ENDOTHELIOMA	2	9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	DOUBTFUL	5	9	—	—	—	—	—	1(Parotid)	1 (ear)	—	1 (testis)	—	—	1 (stomach)	—	1 (breast)
		26	77	TOTAL NUMBER OF HOSPITAL OPERATION CASES FOR MALIGNANT DISEASE ...													
	NON-MALIGNANT.	6	26	—	—	—	—	—	—	—	1	—	4	2	1	1	1
		32	103	TOTAL NUMBER OF HOSPITAL OPERATION CASES EXAMINED IN CANCER RESEARCH LABORATORIES.													

Carcinoma—Males 15, Females 55
Sarcoma „ 4, „ 4
Endothelioma „ 2, „ 9
Doubtful „ 5, „ 9

Operation Cases.

36—40.		41—45.		46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.		81—85.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	2	—	1	—
—	—	—	—	—	1	—	—	—	—	1	—	1	—	—	—	—	—	—	—
—	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1 (rectum)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1 (colon)	—	2 (rectum)	—	—	1 (rectum)	1 (colon)	—	—	—	—	—	—	—	—	—	—
—	—	—	2 (cervix)	—	—	—	—	—	1 (vulva)	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	1(fundus uteri)	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1 (ovary)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	2	—	6	—	3	—	6	—	4	—	6	—	5	—	2	—	—	—	1
—	1	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	2 (jaw bladder)	—	1 (skin)		2 (jaw, (skin)	—	1 (bladder)	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	1 (bladder)									
—		—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	1 (jaw)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1 (femur)			—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—			—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—					—	—	—	—	—	—	—	—	—	—
—	1 (breast)	—	1 (breast)	1 (jaw)	—	—	—	1 (nose)	3 (breast)	—	—	—	4 (cervix, (breast)	—	—	—	—	—	—
2 (kidney, gland)	(Abd. Wall) 2 (breast)	—	—	—	1 (parotid)	—	2 (breast)	—	—	1 (jaw)	—	—	1 (anus)	—	—	—	—	—	—
—	4	—	5	—	4	1	2	1	3	—	—	1	—	—	1	—	—	—	—

TABLE III.

Synopses of Post-mortem Cases.

CARCINOMATA.

No	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
1	H.C. 26/07	M	58	Squamous cell carcinoma of cheek.	Liver.	Double broncho-pneumonia, ulceration of small intestine (non-malignant).	(ii) Universal alopecia.	(i) 6 July '06. (ii) 25 Jan. '07.
2	E.V. 56/07	F	39	? Squamous cell carcinoma. Antrum.	Lung, cervical and bronchial glands.	... ...	(ii) Body thin.	(i) 16 Jan. '07. (ii) 26 Feb. '07.
3	M.W.W. 262/07	F	79	? Spheroidal cell carcinoma of skin.	Skin, liver; supraclavicular, lumbar and iliac glands.	... ...	(ii) Emaciated.	(i) 13 Nov. '07. (ii) 23 Dec. '07.
4	W.F. 149/07	M	48	Squamous cell carcinoma of tongue.	Submaxillary and cervical glands.	Double broncho-pneumonia.	(ii) Much emaciation.	(i) 20 April '07. (ii) 30 June '07.
5	E.G. 166/07	M	56	Squamous cell carcinoma of tongue.	Cervical glands.	Cirrhotic liver, septic pneumonia.	(ii) Emaciated.	(i) 13 April '07. (ii) 28 July '07.
6	P.S. 158/07	M	43	Squamous cell carcinoma of mouth.	None.	Œdema of lungs.	(ii) Some emaciation.	(i) 24 May '07. (ii) 14 July '07.
7	C.S. 27/07	M	54	Squamous cell carcinoma of floor of mouth.	None.	Double broncho-pneumonia.	(ii) Much emaciation.	(i) 11 Oct. '06. (ii) 26 Jan. '07.
8	E.H. 173/07	F	65	Squamous cell carcinoma of floor of mouth.	Submaxillary and cervical glands.	Double broncho-pneumonia.	... ...	(i) 26 June '07. (ii) 10 Aug. '07.

9	W.N. 123/07	M	56	Squamous cell carcinoma of left tonsil.	Cervical glands.	... ...	(ii) Considerable emaciation.	(i) 2 Jan. '07. (ii) 25 May '07.
10	H.M. 78/07	M	46	Squamous cell carcinoma of palate.	Œsophagus, cervical glands.	... ...	(ii) Some emaciation.	(i) 29 Jan. '07. (ii) 6 April '07.
11	J.P. 109/07	M	63	Squamous cell carcinoma of palate.	None.	... ...	(ii) Much emaciation.	(i) 27 Dec. '06. (ii) 9 May '07.
12	A.J. 211/07	M	46	Squamous cell carcinoma of pharynx.	Cervical and bronchial glands.	Great hypertrophy of prostate.	(ii) Very emaciated.	(i) 18 Oct. '07. (ii) 15 Nov. '07.
13	A.C. 249/07	M	57	Squamous cell carcinoma of pharynx.	Cervical glands.	... ...	(ii) Well nourished.	(i) 24 Nov. '07. (ii) 25 Nov. '07.
14	B.E. 244/07	F	25	Squamous cell carcinoma of œsophagus (lower end).	Mediastinal glands.	... ...	(ii) Thin. Hosp. p.m. 213.	(i) 5 July '07. (ii) 18 Nov. '07.
15	H.R. 220/07	M	43	Squamous cell carcinoma of œsophagus (lower end).	None.	Double broncho-pneumonia.	(ii) Great emaciation. Hosp. p.m. 186.	(i) 23 Sept. '07. (ii) 16 Oct. '07.
16	T.B. 238/07	M	48	Squamous cell carcinoma of œsophagus.	Liver, aortic and cervical glands.	Œdema of lungs.	(ii) Much emaciation.	(i) 17 July '07. (ii) 11 Nov. '07.
17	A.J.D. 11/07	M	50	Spheroidal cell carcinoma of œsophagus (middle).	None.	Broncho-pneumonia.	(ii) Great emaciation. Hosp. p.m. 27.	(i) 25 Jan. '07. (ii) 6 Feb. '07. (iii) Gastrostomy.
18	W.H. 171/07	M	50	Squamous cell carcinoma of œsophagus (upper end).	None.	... ...	(ii) Well nourished.	(i) 6 Aug. '07. (ii) 6 Aug. '07.
19	W.B. 111/07	M	58	Squamous cell carcinoma of œsophagus (middle third).	*Mediastinal and *supraclavicular glands.	Ulceration into trachea.	(ii) Extreme emaciation. Hosp. p.m. 87.	(i) 27 March '07. (ii) 10 May '07.
20	J.H. 175/07	M	37	Spheroidal cell carcinoma of body of stomach.	Omentum.	Bronchitis.	(ii) Emaciated.	(i) 19 July '07. (ii) 12 Aug. '07.

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
21	F.B. 110/07	F	40	Spheroidal cell carcinoma of body of stomach.	Ovaries.	Broncho-pneumonia, double pleural effusion, chronic peritonitis.	(ii) Much emaciated.	(i) 4 Feb. '07. (ii) 12 May '07.
22	A.A. 141/07	M	44	Spheroidal cell (colloid) carcinoma of pyloric end of stomach.	Liver.	... ...	(ii) Great emaciation. Hosp. p.m. 112.	(i) 17 May '07. (ii) 24 June '07.
23	M.A.M. 44/07	F	66	Spheroidal cell carcinoma of cardiac end of stomach.	*Liver, *portal glands.	... ...	(ii) Well nourished. Hosp. p.m. 29.	(i) 5 Feb. '07. (ii) 12 Feb. '07.
24	A.G. 39/07	F	40	Columnar cell carcinoma of stomach (body).	Liver, peritoneum.	Gastro-colic fistula.	(ii) Emaciated. Hosp. p.m. 24.	(i) 28 Dec. '06. (ii) 6 Feb. '07.
25	P.O'D. 236/07	M	47	Columnar cell carcinoma of middle of stomach.	Liver, portal glands.	... ...	(ii) Much emaciated. Hosp. p.m. 197.	(i) 26 Aug. '07. (ii) 4 Nov. '07.
26	B.L. 4/07	F	57	Columnar cell carcinoma of stomach (diffuse infiltration).	Peritoneum.	... ...	(ii) Very emaciated.	(i) 4 Oct. '06. (ii) 5 Jan. '07.
27	M.H. 230/07	F	58	*Malignant disease of body of stomach.	R. Kidney.	Left hydronephrosis.	(ii) Very emaciated.	(i) 14 Oct. '07. (ii) 31 Oct. '07.
28	T.C. 232/07	M	63	Columnar cell carcinoma of middle of stomach.	Liver, * portal and * mesenteric glands.	Hypostatic pneumonia.	(ii) Emaciated. Hosp. p.m. 194.	(i) 11 Oct. '07. (ii) 1 Nov. '07.
29	T.H. 159/07	M	50	Columnar cell carcinoma of pyloric end of stomach.	Portal glands.	Hæmorrhage into stomach.	(ii) Thin. Hosp. p.m. 111.	(i) 17 June '07. (ii) 21 June '07.

30	E.P. 240/07	F	47	Columnar cell carcinoma of cæcum.	Mesenteric glands.	Stercoral ulceration at hepatic flexure, perforation.	(i) Two ureters from r. kidney. (ii) Well nourished. Hosp. p.m. 206.	(i) 9 Nov. '07. (ii) 12 Nov. '07.
31	A.E.R. 13/07	F	54	Columnar cell carcinoma of cæcum.	None.	... ...	(ii) Much emaciation.	(i) 19 July '06. (ii) 14 Jan. '07. (iii) Supra-vaginal hysterectomy.
32	A.D.C. 223/07	M	44	Columnar cell carcinoma (becoming transitional) of ascending colon.	None.	... ...	(ii) Emaciated.	(i) 3 July '07. (ii) 21 Oct. '07.
33	A.C. 118/07	M	56	Columnar cell carcinoma of sigmoid flexure.	Peritoneum.	General peritonitis.	(ii) Thin. Hosp. p.m. 93.	(i) 18 May '07. (ii) 20 May '07. (iii) Intestinal anastomosis.
34	W.P. 77/07	M	48	Spheroidal cell carcinoma of rectum.	Liver, brain.	... ...	(ii) Well nourished. Hosp. p.m. 60.	(i) 14 Mar. '07. (ii) 28 Mar. '07. (iii) L. inguinal colotomy.
35	E.A.M. 255/07	F	34	Columnar cell carcinoma of rectum.	Liver, lung, lumbar and bronchial glands.	Œdema of leg, double hydronephrosis, cystitis.	(ii) Emaciated.	(i) 26 July '07. (ii) 14 Dec. '07. (iii) Laparotomy
36	E.S. 14/07	M	41	Columnar cell carcinoma of rectum.	Liver.	Pulmonary tuberculosis.	(ii) Much emaciation. Hosp. p.m. 9.	(i) 29 Oct. '06. (ii) 14 Jan. '07.
37	J.W. 116/07	M	51	Columnar cell carcinoma of rectum	Liver, omentum.	... ...	... ...	(i) 15 Mar. '07. (ii) 19 May '07. (iii) Left inguinal colotomy.
38	E.L. 32/07	F	60	Columnar cell carcinoma of rectum.	None.	Cirrhosis of liver. Cystitis.	(ii) Well nourished.	(i) 10 Jan. '06. (ii) 2 Feb. '07. (iii) Left inguinal colotomy.

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
39	H.W. 59/07	F	66	Columnar cell carcinoma of rectum.	None.	Left hydronephrosis. Ovarian cyst.	(ii) Well nourished.	(i) 14 May '06. (ii) 2 Mar '07. (iii) Left inguinal colotomy.
40	S.H.C. 90/07	M	66	Columnar cell carcinoma of rectum.	Liver.	Double pyonephrosis.	(ii) Emaciated.	(i) 1 Mar. '05. (ii) 18 April '07.
41	J.L. 183/07	M	71	Columnar cell carcinoma of rectum.	Liver.	Œdema of lungs.	(ii) Emaciated.	(i) 9 July '07. (ii) 26 Aug. '07.
42	F.F. 144/07	F	75	Columnar cell carcinoma of rectum.	Liver, lung, adrenal, vertebral column, bronchial and portal glands.	... ...	(ii) Emaciated.	(i) 1 May '07. (ii) 25 June '07.
43	C.L. 85/07	M	45	Colloid carcinoma of omentum.	None.	... ...	(ii) Emaciated. Hosp. p.m. 71.	(i) 22 Jan '07. (ii) 16 Apr. '07. (iii) Laparotomy.
44	L.S. 159/07	F	54	Colloid carcinoma of omentum.	None.	... ...	... ...	(i) 4 Dec. '06. (ii) 16 July '07. (iii) Laparotomy.
45	M.A.O. 209/07	F	79	/ Malignant disease of peritoneum.	None.	... ...	... ...	(i) 8 June '07. (ii) 3 Oct. '07.
46	W.W. 163/07	M	43	* Malignant disease of larynx.	*Cervical glands.	Broncho-pneumonia.	(ii) Emaciated.	(i) 4 July '07. (ii) 21 July '07.
47	T.E.S. 28/07	M	39	Columnar cell carcinoma of left kidney.	Lung, liver, adrenal, pre-aortic glands.	... ...	(ii) Emaciated.	(i) 12 Nov. '06. (ii) 31 Jan. '07. (iii) Exploratory laparotomy.

48	G.R. 216/07	M	47	Malignant disease of left kidney.	Liver, rib.	... ...	(ii) Emaciated. Hosp. p.m. 183.	(i) 24 June '07. (ii) 10 Oct. '07.
49	A.E. 186/07	M	55	Squamous cell carcinoma of bladder.	None.	Left hydronephrosis. Right pyonephrosis.	(ii) Emaciated.	(i) 4 July '07. (ii) 30 Aug. '07. (iii) Supra-pubic cystotomy.
50	K.W. 213/07	F	58	Squamous cell carcinoma of bladder.	Iliac glands.	Gallstones. Abscesses in kidney.	(ii) Much emaciation.	(i) 30 Mar. '07. (ii) 18 Nov. 07
51	M.S. 20/07	F	66	Squamous cell carcinoma of bladder.	None.	Gallstones. Phosphatic urinary calculi (2).	(ii) Much emaciation.	(i) 8 Oct. '06. (ii) 20 Jan. '07.
52	E.M. 215/07	M	46	Spheroidal cell carcinoma of prostate.	Lumbar and inguinal glands.	Gallstones.	(ii) Emaciated.	(i) 7 June '07. (ii) 12 Oct. '07.
53	F.J.A. 219/07	M	61	Spheroidal cell carcinoma of prostate.	Bladder, liver, iliac glands.	... ...	(ii) Emaciated.	(i) 30 May '07. (ii) 16 Oct. '07.
54	W.C. 112/07	M	39	Squamous cell carcinoma of penis	Inguinal glands.	... ...	(ii) Well nourished.	(i) 13 April '07. (ii) 13 May '07. (iii) Amputation of penis.
55	H.S.S. 80/07	M	63	Squamous cell carcinoma of penis.	None.	... ...	... ...	(i) 1 Feb. '07. (ii) 11 April '07.
56	K.S. 92/07	F	28	Squamous cell carcinoma of cervix uteri.	None.	Double hydronephrosis.	(ii) Thin.	(i) 4 Oct. '06. (ii) 21 April '07.
57	A.G. 33/07	F	33	Squamous cell carcinoma of cervix uteri.	Liver, lymphatic glands.	Double hydronephrosis.	(ii) Emaciated.	(i) 16 Nov. '06. (ii) 2 Feb. '07.
58	A.B. 140/07	F	34	Squamous cell carcinoma of cervix uteri.	Bladder, rectum, lung, heart, liver, stomach, spleen, kidney, * peritoneum, pleura, bronchial glands.	Renal calculus.	(ii) Slight emaciation.	(i) 16 April '07. (ii) 22 June '07.

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
59	O.A.H. 1/07	F	36	Squamous cell carcinoma of cervix uteri.	Vagina, rectum, bladder, peritoneum, aortic glands.	Gallstone.	(i) Meso-rectum. (ii) Some emaciation.	(i) 13 Dec. '06. (ii) 2 Jan. '07. (iii) Exploratory laparotomy.
60	V.S. 40/07	F	37	Squamous cell carcinoma of cervix uteri.	Pelvic glands.	Double hydronephrosis.	(ii) Emaciated.	(i) 15 June '06. (ii) 6 Feb. '07. (iii) Hysterectomy
61	A.B. 157/07	F	38	†Malignant disease of cervix uteri.	None.	Broad ligament cyst.	(ii) Much emaciation.	(i) 15 June '07. (ii) 14 July '07.
62	H.E.W. 269/07	F	39	Squamous cell carcinoma of cervix uteri.	Ovary, lumbar glands.	R. hydronephrosis.	... ...	(i) 7 Oct. '07. (ii) 30 Dec. '07.
63	M.W. 263/07	F	40	Squamous cell carcinoma of cervix uteri.	Liver, bladder, rectum; iliac and lumbar glands.	Double hydronephrosis. Vegetations on aortic valves, dilatation and hypertrophy of left ventricle.	(ii) Emaciated.	(i) 20 June '07. (ii) 23 Dec. '07.
64	E.T. 235/07	F	42	*Malignant disease of cervix uteri.	None.	... ...	(ii) Emaciated.	(i) 7 Jan. '07. (ii) 4 Nov. '07.
65	E.B. 99/07	F	47	†Malignant disease of cervix uteri.	† Abdominal glands.	... ...	(ii) Much emaciated.	(i) 15 Sept. '05. (ii) 29 April '07.
66	L.E.S. 170/07	F	47	Squamous cell carcinoma of cervix uteri.	Lumbar glands.	Œdema of right leg. Purulent peritonitis. Double hydronephrosis.	(ii) Much emaciation.	(i) 20 Feb. '07. (ii) 5 Aug. '07.
67	C.D. 181/07	F	47	Squamous cell carcinoma of cervix uteri.	Lumbar glands.	Double hydronephrosis.	(ii) Some emaciation.	(i) 26 July '07. (ii) 18 Aug. '07.

† Included on macroscopic grounds; microscopically, no evidence of malignant disease.

68	E.Y. 18/07	F	48	Squamous cell carcinoma of cervix uteri.	Bladder, liver, spleen, lung, ovary, pelvic and aortic glands.	Left hydronephrosis.	(ii) Some emaciation.	(i) 13 Dec. '06. (ii) 19 Jan. '07.
69	S.T. 88/07	F	49	Squamous cell carcinoma of cervix uteri.	Lumbar glands.	R. pyo-salpinx.	(ii) Some emaciation.	(i) 25 March '07. (ii) 17 April '07.
70	A.J.A. 132/07	F	50	Squamous cell carcinoma of cervix uteri.	None.	Vesico-vaginal fistula. Double hydronephrosis.	(ii) Well nourished.	(i) 4 March '07. (ii) 5 June '07.
71	E.L. 8/07	F	51	Squamous cell carcinoma of cervix uteri.	Aortic glands.	Gallstone. Double hydronephrosis. Cystitis.	(i) Accessory thyroid. (ii) Much emaciated.	(i) 31 Jan. '06. (ii) 9 Jan. '07.
72	S.B. 252/07	F	52	Squamous cell carcinoma of cervix uteri.	None.	Double hydronephrosis. Uterine fibroid. Pneumonia.	(ii) Some emaciation.	(i) 16 May '07. (ii) 10 Dec. '07.
73	E.E.L. 31/07	F	54	Squamous cell carcinoma of cervix uteri.	Peritoneum, pelvic glands.	Right hydronephrosis. Left pyonephrosis. Vesico-vaginal fistula.	(ii) Well nourished.	(i) 4 Jan. '07. (ii) 4 Feb. '07.
74	H.S. 121/07	F	56	Squamous cell carcinoma of cervix uteri.	None.	Double broncho-pneumonia.	(ii) Much emaciated.	(i) 27 March '07. (ii) 27 May '07.
75	J.G. 182/07	F	56	Squamous cell carcinoma of cervix uteri.	Pelvic glands.	Double hydronephrosis.	(ii) Emaciated.	(i) 6 Dec. '04. (ii) 25 Aug. '07.
76	A.H. 156/07	F	62	Squamous cell carcinoma of cervix uteri.	Inguinal glands.	... ...	(ii) Much emaciation.	(i) 19 April '07. (ii) 12 July '07.
77	M.K. 162/07	F	71	Squamous cell carcinoma of cervix uteri.	None.	... ...	(ii) Much emaciation.	(i) 28 Nov. '06. (ii) 19 July '07.
78	L.H. 7/07	F	50	Spheroidal cell carcinoma of cervix uteri.	None.	Broncho-pneumonia.	(ii) Much emaciation.	(i) 27 Jan. '05. (ii) 8 Jan. '07.
79	R.L.S. 150/07	F	44	Columnar cell (becoming transitional) carcinoma of vagina.	Liver, omentum, prævertebral and bronchial glands.	Double hydronephrosis, cystitis, broncho-pneumonia.	(ii) Emaciated.	(i) 6 June '07. (ii) 5 July '07.

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
80	M.J.W. 176/07	F	44	Squamous cell carcinoma of vulva.	Inguinal glands.	... ...	... ...	(i) 10 Feb. '06. (ii) 13 Aug. '07.
81	M.P. 265/07	F	73	Squamous cell carcinoma of vulva.	Liver.	Large uterine fibroid.	(ii) Emaciated.	(i) 20 June '07. (ii) 25 Dec. '07.
82	A.E.M. 268/07	F	31	Spheroidal cell carcinoma of right breast.	Liver, brain; left breast; supraclavicular glands.	... ...	... ...	(i) 27 Feb. '07. (ii) 29 Dec. '07. (iii) Amputation of breast.
83	F.B. 91/07	F	38	Spheroidal cell carcinoma of right breast.	*Supraclavicular glands.	... ...	(ii) Emaciated.	(i) 11 Jan. '07. (ii) 19 April '07.
84	S.A.T. 234/07	F	38	Spheroidal cell carcinoma of right breast.	Liver; left breast.	... ...	(ii) Much emaciated.	(i) 18 July '07. (ii) 2 Nov. '07.
85	E.M.B. 257/07	F	42	Spheroidal cell carcinoma of left breast.	Liver, pancreas, right breast, supraclavicular and lumbar glands.	Uterine fibroids.	(ii) Some emaciation.	(i) 10 Sept. '07. (ii) 17 Dec. '07.
86	E.B. 133/07	F	44	Spheroidal cell carcinoma of left breast.	Lung, liver: cervical, axillary, portal, and inguinal glands.	Solid œdema of left arm. Left pleural effusion. Right broncho-pneumonia.	(ii) Much emaciated.	(i) 16 Oct. '06. (ii) 11 June '07.
87	E.T. 52/07	F	45	Spheroidal cell carcinoma of left breast.	Skin, liver, supraclavicular glands, adrenal.	Broncho-pneumonia. Cirrhosis of liver.	(ii) Emaciated.	(i) 27 Aug. '06. (ii) 24 Feb. '07.
88	C.H. 161/07	F	46	Spheroidal cell carcinoma of right breast.	Brain, vertebræ (Cvii and Di), femur.	... ...	(ii) Emaciated.	(i) 5 March '07. (ii) 17 July '07.

89	L.L.V. 200/07	F	46	Spheroidal cell carcinoma of right breast.*	Liver.	... ...	(ii) Body thin.	(i) 11 Sept. '07. (ii) 13 Sept. '07.
90	E.W. 266/07	F	52	Spheroidal cell carcinoma of left breast.	Liver, lung, skin,* supraclavicular gland.	Double pleural effusion.	(ii) Emaciated.	(i) 15 Aug. '07. (ii) 24 Dec. '07.
91	C.G. 113/07	F	55	Spheroidal cell carcinoma of right breast.	Skin, liver, cerebellum, supraclavicular and mediastinal glands.	Œdema of right arm.	(ii) Considerable emaciation.	(i) 22 Jan. '07. (ii) 13 May '07. (iii) Amputation of breast.
92	H.L. 55/07	F	56	Spheroidal cell carcinoma of right breast.	Lung, liver, adrenals.	Jaundice.	... ...	(i) 25 May '06. (ii) 25 Feb. '07.
93	R.W.. 16/07	F	57	Spheroidal cell carcinoma (cellular type) of right breast.	Liver, lung, brain, kidney; cervical, axillary, mediastinal and abdominal lymph glands.	Right pleural effusion. Broncho-pneumonia.	(ii) Body fat.	(i) 1 Oct. '06. (ii) 16 Jan. '07. (iii) Amputation of breast.
94	R.J. 160/07	F	59	Spheroidal cell carcinoma of right breast.	Skin, peritoneum, liver, adrenal.	Extreme jaundice.	(ii) Emaciated.	(i) 3 April '07. (ii) 16 July '07.
95	E.K. 237/07	F	61	Spheroidal cell carcinoma of right breast.	Skin, left breast, femur, cervical glands.	Double pleural effusion.	(ii) Body fat.	(i) 25 Sept. '07. (ii) 11 Nov. '07.
96	M.B. 151/07	F	61	Spheroidal cell carcinoma of left breast.	Lungs, diaphragm, axillary and bronchial glands.	Broncho-pneumonia, cutaneous nævi.	(ii) Emaciated.	(i) 26 June '07. (ii) 8 July '07.
97	S.W. 193/07	F	65	Malignant disease left breast.	L. cervical, axillary and bronchial glands.	Œdema of left arm.	(ii) Well nourished.	(i) 21 March '07. (ii) 8 Sept. '07.

TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
98	B.W. 136/07	F	65	Spheroidal cell carcinoma of right breast.	Left breast, lung, liver, adrenal, supraclavicular, axillary and bronchial glands.	Gallstones. Uterine fibroids.	(ii) Emaciated.	(i) 11 April '07. (ii) 13 June '07.
99	M.A.B. 174/07	F	65	Spheroidal cell carcinoma of right breast.	Lung, axillary and bronchial glands.	... ...	(ii) Emaciated.	(i) 19 June '07. (ii) 11 Aug. '07.
100	C.D. 254/07	F	74	Spheroidal and columnar cell carcinomata of right breast.	None.	R. broncho-pneumonia, cirrhosis of liver, endarteritis obliterans.	(ii) Not emaciated.	(i) 25 Aug. '06. (ii) 13 Dec. '07.
101	E.T. 198/07	F	75	Spheroidal cell carcinoma of left breast.	Rib, liver, axillary glands.	Gallstones.	(ii) Much emaciation.	(i) 23 Aug. '07. (ii) 15 Sept. '07.
102	S.S. 9/07	F	80	Spheroidal cell carcinoma (cellular type) of right breast.	Axillary glands.	... ...	(ii) Some emaciation.	(i) 6 Oct. '06. (ii) 13 Jan. '07.
				SARCOMATA.				
1	A.T. 137/07	F	21	Mixed cell sarcoma of femur.	External iliac glands.	... ...	... ...	(i) 30 May '07. (ii) 15 June '07.
2	L.A. 64/07	F	42	Mixed cell sarcoma of pharynx.	Tongue, pancreas, cervical glands.	Double broncho-pneumonia.	(ii) Much emaciation.	(i) 1 Feb. '07. (ii) 8 March '07.
3	S.M. 242/07	F	51	Mixed cell sarcoma of pelvis (? secondary to breast amputated in 1904).	Peritoneum.	... ...	... ...	(i) 2 Nov. '07. (ii) 15 Nov. '07. (iii) Amputation of breast.

4	E.B. 81/07	F	51	Small round cell sarcoma of orbit.	Pancreas, uterus, vagina, heart, kidney, cervical and abdominal lymph glands.	Chronic peritonitis.	(i) Well marked pyramidal lobe to thyroid. (ii) Well nourished.	(i) 2 April '07. (ii) 14 April '07.
5	G.S. 74/07	M	63	Round cell sarcoma of lung.	Portal glands.	... ...	(ii) Emaciated. Hosp. p.m. 55.	(i) 28 Feb. '07. (ii) 22 March '07.
6	F.F. 45/07	M	51	Small round cell sarcoma of bladder.	Aortic glands.	... ...	(ii) Body fat. Hosp. p.m. 23.	(i) 21 Jan. '07. (ii) 4 Feb. '07.
7	A.M. 127/07	M	3	Small round cell sarcoma of left adrenal.	Gall bladder.	... ...	(ii) Much emaciation. Hosp. p.m. 98.	(i) 18 May 07. (ii) 30 May '07.
8	R.S. 130/07	F	88	Small round cell sarcoma of right breast.	Lung, liver, pancreas, kidney, adrenal, thyroid, skin, peritoneum, rib; axillary, cervical, lumbar and mesenteric glands.	.. ..	(ii) Emaciated.	(i) 20 April '07. (ii) 3 June '07.
9	M.J. 2/07	F	34	Myxo-chondro-sarcoma of thigh.	None.	... ...	(ii) Much emaciation.	(i) 3 March '05. (ii) 4 Jan. '07.
10	E.M. 256/07	M	42	? Hæmangio-sarcoma of cervical glands.	None.	Cirrhosis of liver.	(ii) Much emaciation.	(i) 18 Nov. '07. (ii) 19 Dec. '07.
11	A.D. 119/07	M	63	Melanotic sarcoma of skin.	Skin, brain, spleen, pericardium; lumbar, portal, iliac, inguinal and bronchial glands.	... ...	(ii) Some emaciation.	(i) 11 Apr. '07. (ii) 21 May '07.

Table III.—Synopses of Post-mortem Cases—*cont.*

ENDOTHELIOMATA.

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
1	Z.E 187/07	F	39	Endothelioma of cervix uteri.	Cæcum, vagina, ovary, peritoneum; inguinal, lumbar, subclavian glands.	... ...	(ii) Emaciated.	(i) 9 Aug. '07. (ii) 1 Sept. '07.
2	M.L. 72/07	F	40	Enthelioma of cervix uteri.	Peritoneum.	Double hydronephrosis. Chronic peritonitis.	(ii) Much emaciated.	(i) 14 Jan. '07. (ii) 22 March '07.
3	A.B. 217/07	F	61	Endothelioma of right breast.	Lung, kidneys, adrenal, peritoneum, vagina, portal glands.	... ...	(ii) Well nourished.	(i) 1 March '07. (ii) 12 Oct. '07.
4	E.S. 50/07	F	78	Peri-enthelioma of left breast.	Lung, liver, right breast, *axillary, * supraclavicular, and * mediastinal glands.	L. pleural effusion.	... ...	(i) 4 Aug. '06. (ii) 20 Feb. '07.
5	M.A.B. 75/07	F	78	Peri-enthelioma of right breast.	Lungs.	Adenoma of adrenal.	(ii) Emaciated.	(i) 1 Feb. '07. (ii) 30 March '07.

A NEW AND RAPID TRIPLE STAIN.

By VICTOR BONNEY,

EMDEN RESEARCH SCHOLAR.

In 1906 ("Lancet," January 27th, 1906; "Virchows Archiv.," 185. Band, 1906) I published an account of a new process of triple staining, in which the stains Saffranin, Methyl Violet, and Orange G were combined in the tissues in such a way that the Saffranin selected the cytoplasmic structures, the Methyl Violet all chromatic substance, and the Orange G the fibrous groundwork.

The process, though yielding good results, was somewhat lengthy, and I subsequently modified it, first by substituting Pyronin for Saffranin, and second by making a mixture of the two principal stains. By these means simplicity of method and certainty have been attained, and the time required has been reduced from an hour to five minutes.

The process is as follows :—

Solutions.

1. Methyl Violet - - - - ·25 gramme.
   Pyronin - - - - - 1·0 gramme.
   Distilled Water - - - - ad 100 cc.

   N.B.—Make the solution by heat and filter. Label "Methyl-Violet-Pyronin Solution."

2. To 100 cc. of Acetone *slowly add, drop by drop, from a drop bottle*, a 2 per cent. aqueous solution of Orange G (made by heat and filtered).

Whilst adding the solution of the stain, keep stirring and rubbing the mixture with a glass rod. When the fluid has attained a pale yellow colour, a faint cloudiness appears. Further addition of the stain increases this until a flocculent precipitate is formed. Continue the addition of the Orange G *drop by drop*, and this precipitate presently redissolves.

Immediately this has taken place, filter into a bottle and label "Orange Acetone."

N.B.—*It is important to add the Orange G solution very slowly, otherwise the precipitate does not appear. After 24 hours a crystalline precipitate appears which augments with time, but the efficacy of the solution is not impaired. After keeping a few weeks its action may be reinforced by the addition of a few drops of the watery solution of Orange G.*

Method.

1. Fix material in Acetic Alcohol (Glacial Acetic Acid F.P. 14 ·7°–15° C. 1 part, Absolute Alcohol 2 parts). Alcohol, or Sublimate Solution, *Chromates and Formalin render the method useless* unless subsequent to staining the sections are treated by oxidising agents.

2. Stain for 2 minutes in the Methyl-Violet-Pyronin solution.

3. Wash rapidly in water, and *wipe all the slide dry*, except the section.

4. Flood the slide with Orange-Acetone—a colour cloud comes out. Pour off and flood again—when no more colour comes out

5. Wash rapidly in pure Acetone, and

6. Transfer to Xylol and mount.

N.B.—Acetone being very volatile, *be careful the slide does not dry.* The Acetone should be kept in a stoppered jar.

Notes.

The whole process should not take more than 5 minutes, and may be done in less. If the preparation be over- or under-stained, return it *through Acetone to water*, and proceed as before until the requisite tints are obtained. All chromatic substance is stained by the Methyl Violet, mitotic figures and nucleoli showing very distinctly, and lymphocytes in which the nucleus is wholly chromatic are rendered very prominent. Keratin, either of surface epithelium or occurring in cell nests in carcinoma, is stained violet.

The cytoplasm of all cells is stained varying degrees of red by the Pyronin. The bodies of plasma cells in particular are vividly stained, and so also are those of epithelial cells, especially when belonging to the deeper layers of a squamous epithelium. The cytoplasm of fixed tissue cells and endothelial cells is less strongly tinted.

The connective tissue framework is stained yellow by the Orange G, as is also the intercellular substance between epithelial cells.

The net result is a marked colour-differentiation of the individual elements of the tissues, which is particularly appreciated when examined by high magnification. The method, on account of its rapidity and simplicity, can be well used in routine work, instead of haematoxylin, over which it presents marked advantages.

It is quite permanent, and may be combined with Weigert's elastic tissue stain if desired. As a test of plasma cells it is equal to Pappenheim's stain, but it does not differentiate mast cells so strikingly. On the other hand, it shows great contrasts between other types of tissue cells which Pappenheim's stain does not.

I have tried it for blood films, but without success.

When working with artificial light, the best results are attained if a blue screen be used.

THE CONNECTIVE TISSUES IN CARCINOMA AND IN CERTAIN INFLAMMATORY STATES THAT PRECEDE ITS ONSET.

By VICTOR BONNEY.

(*With* 28 *Figures in Text.*)

The degree of importance attaching to the changes manifested by the connective tissues in relation with carcinoma has been variously estimated by different observers.

Waldeyer (1) laid great stress on them, and distinguished two phases, namely—the "introducing" changes which he believed play an important rôle in the etiology of the growth, and the "accompanying" change which determined its anatomical structure. In regard to the first of these he remarked that evidence of old connective tissue change is obtainable at the sites of most carcinomata. It is of the nature of an interstitial induration often preceding the malignant growth by many years. There is an increased vascularisation leading to proliferation of the epithelium, the cells of which subsequently become broken up into groups by invading wander-cells from the connective tissue. This epithelial isolation he regarded as the first step in the development of carcinoma.

He thus stated all the essentials of the theory subsequently promulgated by Ribbert, and his conception of the importance of the connective tissue changes is best expressed in his own words—"I do declare now most decidedly that if any kinds of tumours have as regards their etiology and mode of development any relation to inflammatory processes 'tis the carcinomata."

Ribbert (2) examining early cases of carcinoma of the skin noted that in all of them previous changes in the connective tissue could be distinguished. These consisted of a new tissue

due to cell-proliferation which developed between the elastica and the epithelium. The site of the carcinoma to be was therefore elevated. The proliferated connective tissue cells subsequently invaded the tips of the interpapillar processes and separated the individual cells, which, detached from the main mass, acquired an independent power of proliferation whereby they in their turn invaded the altered connective tissue. Subsequent investigation of carcinomata in other situations appeared to him to confirm these observations.

He particularly pointed out that the elongated inter-epithelial or interglandular papillæ seen at the edge of a carcinoma were in their earliest inception not due solely to epithelial proliferation, since the apices of the elongated epithelial processes or glands bore a normal relation to the cutis vera or sub-mucosa. The carcinomatous surface-area, according to him, enlarges by successive conversion of non-malignant epithelium until the entire precarcinomatous area is used up. After this, growth continues by the continued proliferation of the malignant cells already formed, but there is no new conversion.

Ribbert's views have been supported by Borrmann (3), who has made an exhaustive study of carcinomata of the skin. In every case examined by him changes in the connective tissue had preceded the onset of the growth. On the other hand he considers that an actual invasion of the epithelial cells by the connective tissue is rare, and believes that the germinal areas of a carcinoma are to be regarded as cell-complexes isolated in embryonic life.

Ribbert in his latest publication has partly adopted the views of Borrmann, that is to say he believes that the initial process as far as the epithelium is concerned may be in some cases due to a developmental lesion ; but, whether it be due to this or to the changes wrought by inflammation, the foundations of cancerous development are only laid when there has formed a new layer of tissue under the epithelium akin to granulation tissue, by means of which the physiological inter-relationship and interdependence that exists between the epithelium and its subjacent connective tissues is lost.

In contrast to the views of Waldeyer and Ribbert, von Hansemann (4) holds that the primary change in carcinoma is

an anaplasia of the epithelial cell itself, characterised by a new type of mitotic division, an independency of growth, and a power of limitless proliferation. He states that the connective tissue cell-proliferation does not necessarily occur round a carcinoma, though it is usually present, and he noted that the stroma of metastases was often quite different from that of the primary growth. He attributes this to the nature of the tissue in which the growth is taking place and the varying pathological processes to which the stroma is liable. According to him the connective tissue changes are entirely secondary to the epithelial infiltration. His views have been supported by Hauser (5) and Heidemann (6).

Max Borst (7) says that in early carcinomata changes of an inflammatory nature are always present. A real proliferation of the connective tissues is much less frequent. Whilst regarding these changes as largely reactive, he admits that they are also in some cases the special cause of the new growth. It is true, he says, that the interepithelial papillæ are elongated by proliferation, but the epithelial processes are more than correspondingly elongated, and they must also therefore be proliferating. True isolation of epithelial cells such as described by Ribbert is a rare occurrence. The primary stroma is either composed of the pre-existing cells and tissues, or is newly formed as in the papillary and villous carcinomata. The stroma of metastases varies according to the tissue in which the metastasis is growing; on the whole it resembles that of the primary growth.

Borst therefore appears to hold views intermediate between those of Waldeyer and Ribbert on the one hand, and von Hansemann on the other; i.e., he allots to both epithelium and connective tissue a primary share in the process. He states that the cell infiltration and proliferation at the edge of a carcinoma is harmful, and that it prepares the way for its further extension.

Fischer endeavoured to produce in the subepithelial tissue of a rabbit's ear changes in the connective tissue comparable to those described by Ribbert in human carcinoma. After trying many substances he found that the repeated injection of a solution of the stain Scharlach R in Olive Oil produced not only an increase in the number of connective tissue cells,

but also led to great epithelial hypertrophy, terminating in definite downgrowth. The epithelial cells exhibited abnormal mitoses. According to him the connective tissue changes were not the cause of the epithelial proliferation, but were coincident with it, and he attributed it to the effect of an "attraxin" contained in the Scharlach oil. The process, however, stopped short of malignancy, and he pointed out that it was therefore evident that some additional factor was required to produce a carcinoma. His paper is of great value and marks a distinct advance in the experimental investigation of the causes of carcinoma.

Wakelin-Barrett has confirmed Fischer's work. He believes, however, that the subepithelial tissue changes are secondary to the epithelial ingrowth, since they did not occur when the Scharlach oil was injected into areas of connective tissue not adjacent to epithelium. He endeavoured to produce artificial metastases of the thickened epithelium by implanting grafts into various situations, but was unsuccessful.

Bashford and Murray have shown conclusively that the stroma of mouse-cancer is a product of the tissues of the host, and is not derived from the implanted tissue. Their results are of much importance as applied to the study of secondary nodules, since mouse-carcinoma grafts are to be regarded as experimental metastases.

The literature bearing on the connective tissue changes in connection with carcinoma is so large that the foregoing very brief résumé of the work and views of some of the principal investigators must suffice.

I shall now pass to my own work, which is founded upon material drawn from a large number of carcinomatous growths removed from various situations and from certain inflammatory states which commonly precede the onset of carcinoma. With this has been compared the normal histology of the tissues from the same parts, together with the histological features characterising inflammatory processes not directly concerned in the production of carcinoma. I have specially studied the histology of very early carcinoma whenever such specimens have been available. In the course of this investigation I have made use of a large number of differential tissue stains, but I have particularly relied on

three of them, namely : (1) Pappenheim's Plasma Cell Stain, (2) Weigert's Elastic Tissue Stain, and (3) my own process of Triple Staining, an account of which originally appeared in Vol. VI. of the Archives of the Middlesex Hospital, but which I subsequently modified in accordance with the description published at the last meeting of the Pathological Society of Great Britain and Ireland.

GENERAL SURVEY OF THE CONNECTIVE TISSUE CHANGES IN PRIMARY CARCINOMATA.

The Cellular Elements.

If the cloud of connective tissue cells surrounding an early primary carcinoma (the so-called zone of small round cell infiltration) be studied by the aid of differential stains, it will be found that it contains a large number of cell types.

These are as follows :—

The Lymphocytes.—*Situation.*—Lymphocytes are a conspicuous feature of the cell proliferation surrounding an early carcinoma. (Fig. 1.) They are especially aggregated at the tips of the epithelial processes, where they may be seen intercalating themselves between the individual epithelial cells.

FIG. 1.—Principal cell types seen in the connective tissue in carcinoma. A. Lymphocyte. B. Lymphocyte exhibiting chromatic network. C. Plasma cell. D. Fixed tissue cells. E. Endothelial cell. F. Mast cell

At the points of maximum aggregation, especially in squamous cell carcinoma, they invade the epithelial processes to such an extent that the epithelial edge becomes quite broken up, and the demarcation between epithelial and connective tissue elements is obscured. As one passes into the older portions of the growth they become less numerous, until in the oldest parts they may be absent altogether.

Origin.—The origin of these lymphocytal aggregations is very difficult to decide. As will be shown later, their first appearance precedes that of the growth itself. Division either by mitosis or amitosis is never to be observed in them.

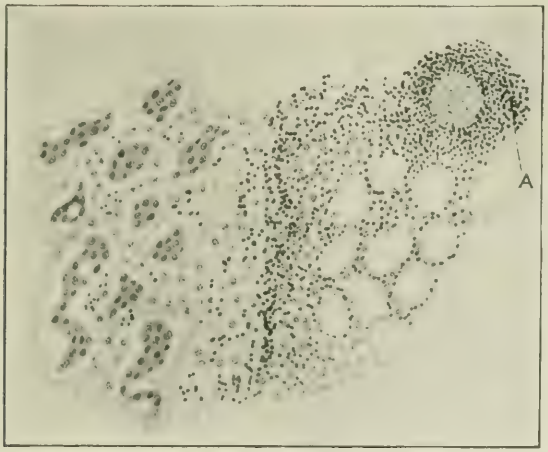


FIG. 2.—Edge of a carcinoma of the breast, showing at A a new lymph node with a well-marked germinal area.

They lie free within the spaces of the tissue network, and I have been unable to find definite transitional forms between them and endothelial cells on the one hand or plasma cells on the other. If not formed by the tissues on the spot, these cells must have been borne thither by the blood stream or have found their way along lymphatics. As regards the first a certain number of lymphocytes are seen in the hæmic capillaries, but not in the quantity one would expect if their origin were solely from this source. They are much more numerously seen in the perivascular lymphatics, and it is by this route that they probably reach the site of the growth.

It is certain that the lymph glands in the vicinity of a carcinoma are in a state of enlargement and activity. They contain big germinal areas containing many mitoses. Further, it is certain that new lymph nodes appear in the tissues surrounding a carcinoma. Ribbert has laid stress on these. I have encountered them many times. That they are true nodes and not mere aggregations is proved by their exhibiting well-formed germinal areas with mitoses. (Fig. 2.)

Fate.—I find no evidence that these cells undergo destruction or metamorphosis during their contact with the epithelial cells. Certainly they take no part in the formation of the stroma of the growth. Contrasting their large numbers at the periphery of the growth with their sparsity in the older portion, it is strongly suggested that they are being pushed back by the advancing epithelial cells. If the lymphocytes retire from the tissue meshwork before the advancing epithelial cells it is possible that they are translated along the lymphatics to the next gland of the series, and thus in part occasion the enlargement without epithelial invasion which is seen in the glands at the periphery of a carcinomatous area.

It is noteworthy that in spite of the marked lymphocytosis in the area of the growth, Price-Jones has shown that there is no increase in the mononuclear content of the blood at large until a very late stage of the disease, and then only very slightly. (These Archives, Vol. I., p. 113.)

Amongst these lymphocytes are seen some which when stained by my method exhibit a peculiar appearance. They are rather smaller than usual, and present a fine black coloured network within the substance of the nucleus. I am at present unable to state what is the significance of this, but I have seen them in other inflammatory conditions. (Fig. 1.)

Plasma Cells.

These cells are the most striking objects seen in the connective tissue in the neighbourhood of a carcinomatous growth. They present a large cell body, round or oval in form (unless subject to compression), with a round eccentric nucleus containing five to eight periphery-placed masses of

chromatin and one or two centrally-placed nucleoli, and they possess fine processes which unite them to other plasma cells. (Fig. 1.)

Situation.—They are rarely found in immediate contact with the epithelial cells, and they never intercalate themselves between them; the zone immediately surrounding the epithelial cells is, as a rule, occupied by lymphocytes and endotheloid cells only.

The plasma cells lie beyond this zone and are mixed at first with lymphocytes, but further outside still they are seen in large and unmixed aggregations often at a very considerable distance from the growth. In the early specimens of carcinoma that I have examined they are already present in large quantities. They proliferate in rows, producing rifts in the previously homogeneous fibrous tissue, which in time completely disappears. They appear to divide by amitosis chiefly, binucleate cells being commonly seen, but mitoses are sometimes observed.

Origin.—The origin of these cells is very obscure. They are practically not present in normal tissues. There is no evidence that they are derived from lymphocytes. Indeed, if a lymphatic gland the seat of carcinomatous invasion be examined, it is noted that the plasma cells lie in the stroma of the gland towards and in its capsule, and quite distinct from the lymphocytes.

With regard to a possible origin from endothelial cells, it is difficult to believe that endothelial cells become converted into plasma cells in view of the very distinctive character of areas of endothelial proliferation. It is true that collections of plasma cells are frequently met with around small vessels and capillaries. But on close examination it will be found that an endothelial lining and two or three layers of endothelial cells intervene between them and the lumen of the vessel. Occasionally lymphatic channels may be seen whose walls appear to consist entirely of plasma cells, but it must be remembered that the finest ramifications of the lymphatic system do not possess an endothelial lining. Large aggregations of plasma cells frequently surround well-formed vessels, and Whitfield (11) has suggested that they may spring from the endothelium of the perivascular lymphatics.

The theory of Grawitz, which states that, in resting conditions of the connective tissue, certain cells may become invisible to become again visible when an appropriate stimulus causes them to proliferate, is most applicable to the origin of plasma cells.

My own observations incline me to derive their origin from certain elongated small nuclei visible in resting connective tissue, which differ from the nuclei of ordinary fixed connective tissue cells in being smaller and more chromatic. If the periphery of an area of plasma cell proliferation stained by my method be closely examined, certain elongated streaks stained by the Pyronin will be seen. All gradations between them and fully formed plasma cells may be traced. Heidemann, who supports Grawitz's "slumber-cell" theory, has noted the same appearances in sections stained by Saffranin. I originally used Saffranin in my staining method, and entirely corroborate him.

Fate.—I find no evidence that plasma cells undergo active destruction by the ingrowing epithelial cells. They retain their position in the stroma longer than the lymphocytes. The delicate processes uniting them to other plasma cells would prevent regression before the advancing growth. On the other hand there are frequent appearances suggesting that these cells can become elongated to produce some of the cells of fibrous tissue. In the process of elongation their cytoplasm loses its distinctive staining properties and the nucleus becomes hyaline and reticular. Thus it is probable that they, together with the fixed connective tissue cells, constitute the framework of the stroma on which a collagenous deposit subsequently occurs. In the oldest portions of the stroma they, with all the other cells there, appear to undergo pressure atrophy.

Endothelial Cells.—The part played by endothelial cells in carcinoma appears to be small if one limits the term "endothelial" to those cells definitely lining blood and lymph channels. True endothelial proliferations are seen occasionally around small blood vessels. There is no evidence that they metamorphose into any other type of cell, the cell mass remaining distinctively hyaline. (Fig. 1.)

Leucocytes.—Polynuclear leucocytes are very slightly in evidence in a carcinomatous area under uncomplicated conditions. In sections stained by Leishmann's method, a considerable number of them are seen within the hæmic capillaries, but diapedesis is unusual. In ulcerating growths, however, a considerable number may be seen outside the vessels, especially where the epithelium is degenerate, as in a cell nest, where they may be aggregated between the flattened epithelial cells. All these leucocytes exhibit fine eosinophile granules in their cytoplasm.

The Fixed Connective Tissue Cells.—On the assumptions (1) that normal connective tissue consists of a meshwork of branching fibres surrounding a number of irregular spaces, in relation to which are seen hyaline nuclei, round or elongated in shape according to circumstances; and (2) that in inflammatory conditions this meshwork becomes largely obscured by the number of additional cells brought to or produced in the part, I believe that the fixed connective tissue cells play a relatively unimportant part in the tissue changes associated with carcinoma. (Fig. 1.)

Certain of them probably give rise to plasma cells, as we have seen. For the rest an increase in their number undoubtedly occurs, and mitosis is observed occasionally. Their increase is most obvious in the papillomatous types of carcinoma, where an undoubted elevation of the connective tissue occurs. It is to be noted, however, that even in this type of growth the vast bulk of the warty mass is due to enormous epithelial proliferation, while the intra-epithelial papillæ, though abnormally elongated, are also abnormally narrowed.

They are seen best in the older parts of the stroma, for here they are not obscured by the cloud of plasma cells and lymphocytes which crowd the growing edge. They possess fine processes (fibroglia fibres) which anastomose and make up the characteristic retiform structure of the stroma. In the oldest parts of the stroma the nuclei appear to be undergoing a pressure atrophy, so that fibres only are found here.

Mast Cells.—Mast cells are frequently to be observed in the neighbourhood of a carcinoma. On the other hand they are present in normal tissues, as for example the breast, where

large numbers of them can be found. I have not been able to satisfy myself that they are necessarily increased in number in a carcinomatous growth area. (Fig. 1.)

Giant Cells.—I have not been able to find giant cells of connective tissue origin in the area of a carcinoma, though they have been described by Becher and others. Becher (12) stated that they were "foreign body cells" produced by the presence of degenerate or dead epithelium, and that their presence indicated a tendency to natural cure. They must be rare, since I have not once seen them in the course of an examination of a very large number of specimens.

Their absence in carcinoma is very striking, seeing the frequency with which they are met in association with necroses,

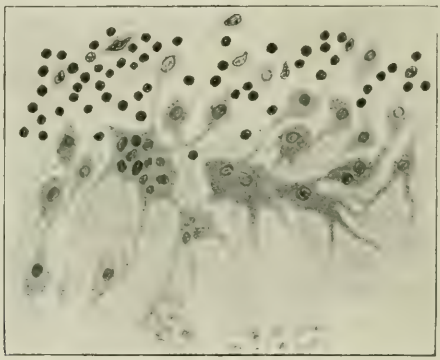


FIG. 3.—Edge of experimental implantation of human carcinoma into the peritoneal cavity of a rabbit, showing histioclasis by giant cells.

foreign bodies, and experimental implantations, conditions in which a protective destruction of the offending substance is in progress.

In experimental implantations of human carcinoma into rabbits that I have carried out, these giant cells are very striking objects in the cell reaction which in a short time circumscribes the implanted tissue. They lie against and in the implanted tissue, and are evidently destroying it. (Fig. 3.)

The White Fibrous Tissue.

A study of white fibrous tissue founded upon its formation in scars and its disintegration in inflammatory states shows

that it consists of a groundwork of fibrils to which the term "fibroglia" has been well applied. These fibroglia fibres are prolongations of the fixed connective tissue cells which anastomose with one another and form a fine meshwork. Deposited around or on these is a collagenous matrix on which the density of the white fibrous tissue appears to depend. Thus in old scars it is present in large quantity, obscuring the cell elements and fibroglia fibres, whilst in all conditions of cellular rarefaction it disappears, and the fibroglia fibres and cells are unmasked. This rarefaction of white fibrous tissue, due to disappearance of collagen, occurs in all conditions of connective tissue cell aggregation.

At the edge of a primary carcinomatous area this rarefac-

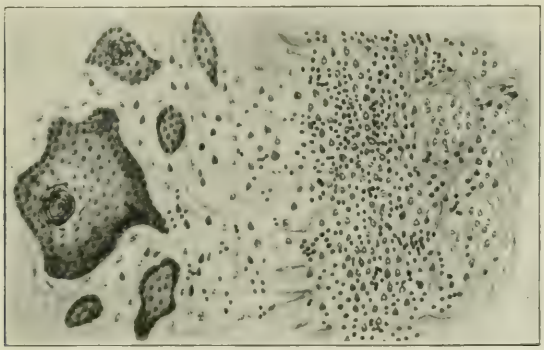


FIG. 4.—Edge of a squamous cell carcinoma, showing transformation of the connective tissue into the stroma of the growth at the zone of tissue cell proliferation.

tion of the tissues by the dense aggregations of lymphocytes and plasma cells is seen in progress. (Fig. 4.) The plasma cells in particular by their proliferation produce rifts in the previously homogeneous collagenous matrix, and this is occurring in many areas at a considerable distance from the growth.

At the margin itself the fibrous elements become quite obscured by the cloud of lymphocytes and plasma cells. As one passes nto the more central portions, the cell aggregations (particularly the lymphocytes) disappear, and unmask the decollagenised fibroglia fibres, which with the hyaline connective tissue cells and the elongated and atrophying plasma cells

make up the stroma of the growth. The general effect is a characteristically loose and hyaline connective tissue, staining ill with protoplasmic or nuclear stains, and consisting, I believe, of altered plasma cells and the original fibroglia fibres and cells of the part from which all the collagenous material has been removed by the preceding cell proliferation.

At a later stage still, and particularly in the slower-growing forms of carcinoma, collagen is again deposited around the fibroglia fibres, and the stroma becomes dense and in appearance almost acellular.

The Yellow Elastic Tissue.

Melnikow-Raswedenkow,(13) Abel,(14) and Goldmann(15) found that there occurred a progressive disappearance of elastic tissues in the stroma of Carcinoma, and Wrench(16) in the laboratories of the Middlesex Hospital Cancer Investigation Department came to a similar conclusion. On the other hand Fischer(17) found in certain areas of Carcinoma of the Breast large aggregations of a granular-looking elastin, whilst it was absent in other parts. He considered that these aggregations were due to a new formation. New formation of elastic tissue in malignant growths has also been reported by von Hansemann,(18) Lubarsch,(19) Polak-Daniels,(20) and Meinel.

Tsutomu Inouye,(21) investigating twenty cases of gastric carcinoma, found that whilst generally speaking there is a disappearance of these fibres, yet here and there accumulations of them could be found which he regarded as of new formation. Tores(22) has described a new formation in fibrous tumours, whilst Melnikow-Raswedenkow and Williams proved it in certain chronic fibratic states (e.g. cirrhosis of the liver). These observations were confirmed by Wrench.

My own investigations show that in all areas of connective tissue cell proliferation there is a coincident disappearance of the elastic fibres. Thus they disappear early in tuberculous and syphilitic inflammation, in other chronic granulomatous processes, and in the leukoplakias; nor does regeneration occur in the stage of scarring or fibrosis. Elastic tissue also disappears

in certain conditions not associated with a marked proliferation of the tissue cells. Thus it is absent from the scars of healthy wounds, although, as I shall show later, there is little cell proliferation to be observed in the course of this process. Further it tends to disappear in areas which have been frequently exposed to the action of X-rays, and it may undergo a simple pressure atrophy under the thickened epidermis of a corn. Lastly a disappearance of it occurs in senile skin.

Excluding the three last conditions, however, its absence from an area in which it normally occurs unassociated with a present tissue cell proliferation is a certain sign of old inflammatory change.

In certain chronic irritative states, which however presumably fall short of producing a cell proliferation, its quantity may be actually increased. Thus under the skin of a lip which presented a hypertrophy of the epithelium as a result of chronic irritation an abnormal quantity of granular-looking elastin was found, and I have noted similar appearances in the neighbourhood of several rodent ulcers.

In the area of early primary carcinoma there has already occurred, as I shall presently show, a complete disappearance of yellow elastic tissue as a result of a pre-existent chronic inflammatory process. It is into this de-elasticised area that the first epithelial downgrowths occur. Outside this area of previous disappearance a further destruction occurs by the plasma cell and lymphocytal proliferation which is going on beyond the limits of the epithelial cells. A few of the elastic fibres in this zone, however, escape destruction, and subsequently, as the growth progresses, come to lie in the stroma, where they appear to be subject to a pressure atrophy and finally disappear, so that the oldest parts of the stroma contain no elastic tissue at all.

It is, however, to be noted that in occasional specimens of carcinoma large aggregations of elastic tissue are present in isolated spots within the stroma. This is best seen in certain carcinomata of the breast, where they appear to surround the pre-existent ducts and large vessels which have become included in the growth but not destroyed by it. Though a certain amount of this elastic tissue may be due to condensa-

tion of previously existing fibres by the pressure of the epithelial masses, yet the quantity of elastin present is so large as to suggest that some of it is newly formed. Moreover, it is granular and structureless, as Fischer pointed out. (Fig. 5.)

To sum up, then, elastic tissue disappears in all cases of connective tissue cell proliferation, whether this be associated with a definite inflammatory state, or with the connective tissue changes that are going on in a carcinomatous area. This disappearance is permanent, i.e. there is no regeneration of the elastic fibres when the cell proliferation has departed and fibrosis has supervened, which statement applies equally

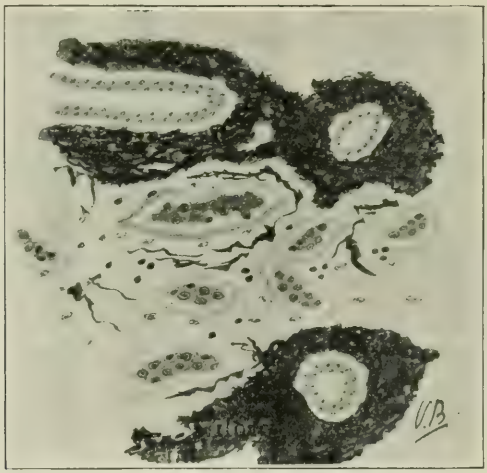


FIG. 5.—Carcinoma of the breast, showing enormous aggregations of granular elastin (Weigert's stain).

to the older parts of the stroma of primary carcinoma and the fibrotic stage of chronic granulomatous inflammation.

In certain conditions, however, of chronic irritation which fall short of producing cell proliferation in the connective tissues, yellow elastic tissue may be increased by the deposition of a granular elastin around the old fibres. This is seen in some simple irritative states as well as in isolated areas in the stroma of carcinoma.

A STUDY OF THE CONNECTIVE TISSUE IN PRIMARY CARCINOMA OF PARTICULAR SITES AND IN CERTAIN INFLAMMATORY STATES WHICH PRECEDE ITS ONSET IN THEM.

Having now reviewed the changes exhibited by the connective tissue in relation to primary carcinoma in general, it is necessary to consider these changes as applied to primary carcinoma in particular situations, and specially to study certain inflammatory states which clinically so often precede the development of the growth as to warrant their being termed precarcinomatous.

Carcinoma of the Vulva.

The association between the chronic inflammatory condition known as leukoplakia of the vulva and carcinoma was first noted by Hulke and Henry Morris, and Bland-Sutton and Butlin have remarked on the frequency of this occurrence. A clinical investigation of a large number of cases shortly to be published by Comyns Berkeley failed to find one example of carcinoma of the vulva in which this condition was not antecedent to the onset of the new growth. I have microscopically studied material from a large number of these cases with the following results.

In the early stage of the affection there occurs a marked hyperæmia of the subepithelial tissues, and a number of thin walled blood spaces become apparent. At the same time a connective tissue cell proliferation takes place; at first of lymphocytes only, but later of plasma cells as well.

The lymphocytes are aggregated immediately under the epithelial margin, and particularly at the tips of the intrapapillar processes. Here they are seen intercalating themselves between the epithelial cells, in places in such quantity as to fairly break up the epithelial edge and to render the demarcation between connective tissue and epithelium indistinct. (Fig. 6.) Deeper down lymphocytal aggregations are seen. These usually surround small vessels, which however only contain polynuclear leucocytes as a rule. Here and there in

the connective tissue are seen new lymph nodes with germinal areas similar to those found in the neighbourhood of a carcinoma. (Fig. 7.) There is no evidence of degenerative changes in these lymphocytes, but certain of them exhibit the peculiar black nuclear network to which I have already referred.

The plasma cells are seen proliferating in rows along rifts in the fibrous connective tissue. They are situated often at a considerable distance from the epithelial margin, nor do they ever intercalate themselves between the epithelial cells.

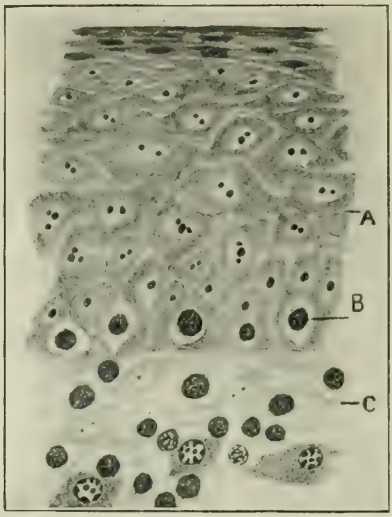


FIG. 6.—A portion of a leukoplakic vulva under high magnification, showing lymphocytal intercalation. A. Epithelial cells. B. Intercalated leucocytes. C. Lymphocytes and plasma cells in the subepithelial tissue.

The fixed connective tissue cells do not show marked changes, though it is probable they too are somewhat increased in number. Endothelial proliferation does not occur to any extent, and polynuclear leucocytes do not apparently play much or any part in the process.

As a result of the plasma cell and lymphocytal proliferation there occurs at first a marked rarefaction of the connective tissue, due to a disappearance of collagen and elastin. The fibroglia fibres become more apparent, and the yellow

elastic fibres disappear, so that the thin walled blood channels in the subepithelial tissues are without an elastic tunic.

The epithelium becomes much thickened, and keratinisation becomes a marked feature in the more superficial epithelial cells, whereas in the normal vulval epithelium it is almost absent. The subepithelial papillæ are elongated by the connective tissue proliferation, whilst the interpapillar epithelial processes are correspondingly lengthened. Thus we have under the thickened epithelium a practically new formation made up of a large number of new tissue cells

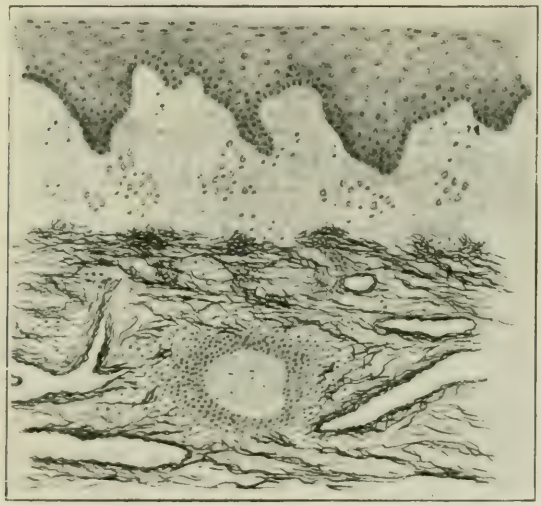


FIG. 7.—Leukoplakia of the vulva, showing the complete disappearance of the elastic tissue under the epithelium, and a new lymph node with a well-marked germinal area in the subepithelial connective tissue.

together with the de-elasticised and decollagenised pre-existent elements. (Fig. 7.)

In the older and quiescent stages of leukoplakia of the vulva the cell aggregations disappear and collagen is redeposited in abnormal amount in the subepidermal tissues, so that we then see a much-thickened and extensively keratinised epidermis resting on a peculiarly dense connective tissue, from which, however, all yellow elastic elements are absent. This stage might be regarded as a state of healing, but there

is no true cure in the sense of a return to the normal, the relation between epithelium and connective tissue having been permanently altered.

My specimens, however, and clinical evidence also, support the view that carcinoma is much less likely to develop in this stage than in the preceding one, and then only when for some reason the tissues have taken on a renewed cellularity. In the larger number of cases in which carcinoma develops, it would appear to do so over an area which has never attained this resting stage, but in which active tissue cell proliferation has gone on up to the beginning of the malignant process. For in my earliest cases, in which the epithelial downgrowth is only as yet foreshadowed, the

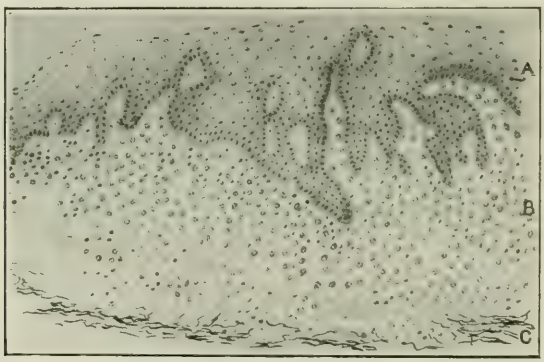


FIG. 8.—The earliest beginnings of carcinoma of the vulva. A. Downgrowing epithelium. B. De-elasticised subepithelial tissue crowded with plasma cells and lymphocytes. C. Unaltered elastic fibres.

connective tissue cell proliferation around this area is already typical, and clinically when carcinoma develops in the quiescent stage it does so in some small fissure or erosion which had refused to heal.

The beginnings of carcinoma are seen over an area of variable extent, large and diffuse when it commences in the earlier stages of leukoplakia, but small and localised when it begins in its later phases. The carcinomatous change begins as a great hypertrophy of the interpapillar processes over a certain area, whereby they penetrate more deeply than normal into the underlying connective tissue. The connective tissue papillæ are, however, more than correspondingly

elongated, so that they reach much higher than normal, but they are thinned and compressed. The connective tissue shows a great cell proliferation of the type I have described as occurring both in the earlier stages of leukoplakia and outside the margin of fully developed carcinoma. (Fig. 8.) It is particularly to be noted that the earliest downgrowth of the epithelium is into a tissue deficient in yellow elastic fibres and otherwise profoundly altered by the pre-existent inflammatory process. (Fig. 9.)

As the growth advances the surface epithelial cells do not keratinise completely, and become loosened in their attachment to surrounding epithelial cells. Many probably desquamate, and eventually the elongated connective tissue

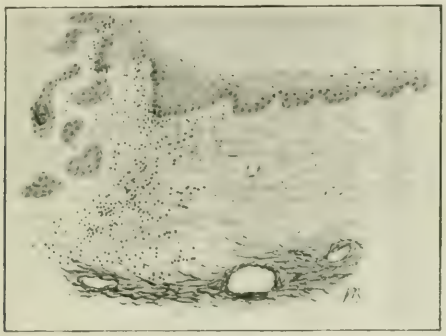


FIG. 9.—Carcinoma of the vulva superimposed upon an old leukoplakia of the vulva, showing the epithelial downgrowth into the altered subepithelial tissue.

papillæ reach the free surface. The surface of the growth now bleeds readily, and its condition may be likened to the skin after a Thiersch graft has been removed. Later still the epithelial downgrowths, which at first are simply the enlarged pre-existing interpapillar processes of the epidermis, become branched and tortuous.

The surface extension of the growth is at first by successive conversion of hypertrophied processes into definite carcinomatous downgrowths, and this seems to continue, as Ribbert stated, until the whole "precarcinomatous" area is exhausted. After this my investigations show that the growth continues by division of the cells already formed, but

that there is no conversion of normal epithelium into carcinoma cells.

All carcinomata of the vulva are raised at their commencement, this elevation being due partly to proliferation of the epithelial cells, partly to the elongation of the papillæ, and partly to the connective tissue cell multiplication that is going on under the epidermis. In the papillomatous types this elevation is very marked. The vast bulk of these projecting masses is, however, epithelial, the connective tissue papillæ being extremely elongated and thin, and showing signs of pressure atrophy. In my specimens of the papillomatous type of growth there is less evidence of profound changes in the subepithelial connective tissues than in the commoner or ulcerative variety; for though lymphocytes are present in large numbers, plasma cells are much scarcer, whilst the elastic tissue has not been destroyed to the same extent. Clinically the prognosis of this form of growth is better than that of the ulcerative form.

Carcinoma of the Tongue.

From the clinical standpoint most cases of carcinoma of the tongue exhibit well-marked evidence of pre-existent inflammation changes in the affected organ. In the larger number of these the tongue is definitely leukoplakic. Pathologically all the cases that I have examined have apparently arisen as an epiphenomenon to a condition of chronic inflammation.

In the earlier stages of chronic superficial glossitis the subepithelial connective tissue becomes crowded by a number of lymphocytes which are especially aggregated at the tips of the interpapillar epithelial processes, and are here seen intercalating themselves between the individual epithelial cells. This process of intercalation particularly affects the Malpighian layer. The "basement membrane" is usually intact, the cells having apparently passed through it. At the points of maximum lymphocytal aggregation, however, the epithelial edge becomes much broken up, and the definition between epithelium and connective tissue is obscured. The distribution of these lymphocytal aggregations is, however, unequal,

many of the epithelial processes being slightly affected, whilst around others enormous collections have occurred.

Deeper down are seen quantities of plasma cells proliferating in rows or masses. As in leukoplakia of the vulva, these cells do not often occur immediately under the epithelial margin, but are situated some slight distance from it. Superficially they are mixed with lymphocytes, but lower down they are "pure." (Fig. 10.)

The hyaline connective tissue cells show evidence of multiplication, and the connective tissue papillæ are enlarged and elongated. The apices of these papillæ are usually free of lymphocytes and plasma cells, and show the hyaline cell only.

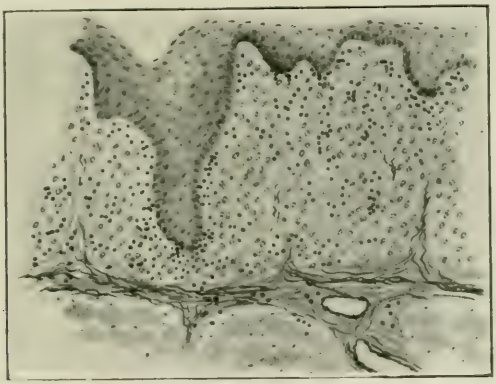


FIG. 10.—Acute leukoplakic inflammation of the tongue, showing the loss of elastic fibres under the epithelium, and the proliferation of plasma cells and lymphocytes.

Coincidently with the proliferation of these various types of cell, a great rarefaction of the subepithelial connective tissue takes place, and the yellow elastic fibres which are present in large quantity in the normal organ disappear, whilst the epithelium becomes thickened, and the keratinisation of the superficial layers is exaggerated.

In the older or quiescent stages the hypercellularity disappears, much collagen is deposited, and the subepithelial connective tissue becomes dense and fibrous: but there is no regeneration of the elastic tissue. The papillæ shrink and the epithelium becomes much more of a flat sheet. In the

oldest stages it becomes less thickened and the cells undergo early keratinisation.

In any of these stages it is apparent that the epithelium is resting on a much-altered and largely new subepidermal tissue, and comparing these changes with those I have already described as occurring in leukoplakia of the vulva it is seen that they are identical.

In the earliest carcinomata of the tongue that I have examined the down-growing epithelial columns are continuous with hypertrophied interpapillar processes, and are growing down into a subepidermal tissue already the seat of the changes I have just described. Surrounding the epithelial masses is a connective tissue cell proliferation identical in quality with that seen in chronic glossitis. The general relations of the connective tissue cells to the epithelial cells and the composition and arrangement of the stroma are similar to those already described in the general survey.

Carcinoma of the Lip.

A relation between carcinoma of the lip and chronic irritation is recognised. This irritative process is limited to a comparatively small area in most cases. Hence in endeavouring histologically to ascertain the relation borne by the carcinoma to any antecedent inflammatory process very early specimens are alone of value. For in more advanced cases the whole precarcinomatous area is already taken up by the growth and all evidence of pre-existent change is destroyed.

In a specimen the size of a small split pea the following appearances are present. Microscopically the surface is covered by a thin squamous epithelium, which at the periphery of the nodule is seen to be sending downwards multiple epithelial processes of large size into the underlying connective tissue. These processes are unbranched and well defined, and would not ordinarily be termed carcinomatous, though they constitute the earliest changes in the production of malignancy. (Fig. 11.)

The subepithelial tissue into which they are projecting is practically a mass of plasma cells and lymphocytes. The lymphocytes are aggregated around the tips of the epithelial processes, whilst the plasma cells cover a wider area at whose

periphery many isolated groups are seen, the cells of which lying in rows or masses are producing rifts in the connective tissue matrix.

The connective tissue lying beyond the area of tissue cell proliferation is seen when stained by Weigert's method to be totally deficient in elastic tissue, and to be composed of a dense homogeneous collagenous fibrous tissue with a few hyaline connective tissue cells lying in it. Such an appearance is the result of a pre-existent inflammatory change corresponding to the quiescent stages of leukoplakia of the vulva or tongue.

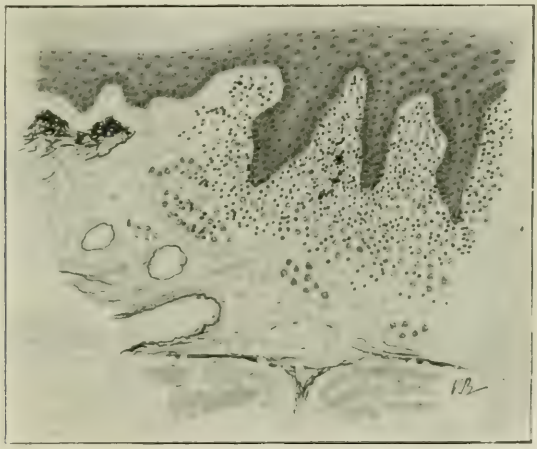


FIG. 11. Edge of a small carcinoma of the lip. The epithelial processes are growing into a tissue already deficient of elastic fibres and the seat of a large plasma cell and lymphocytal proliferation. To the left is seen a quantity of granular elastin under the non-malignant epidermis.

This de-elasticised area extends beyond the area of plasma cell proliferation for about the same distance as that area itself occupies, and it reaches under the epithelium for some distance beyond the most peripherally-placed epithelial downgrowth. Under the epithelium beyond this is seen an abnormally large amount of elastic tissue, for the most part granular and ill-arranged, and the epithelium here is unduly thickened and keratinised. This condition is also due to a chronic irritation which has never reached an intensity sufficient to produce tissue cell proliferation.

Sections taken from the centre of the growth show typical carcinomatous downgrowths occurring into a tissue the seat of old inflammatory changes. These downgrowths are enlarged and branched interpapillar processes, and they are surrounded by a dense mass of plasma cells and lymphocytes. The relatively large area occupied by the tissue cell proliferation is a point to which I shall have occasion to refer later.

Carcinoma of the Cervix.

Carcinoma of the cervix bears clinically a striking relation to the inflammatory conditions of the cervix consequent on childbirth. Pathological evidence of pre-existent cervicitis and "cervical erosion" is present in all the early cases which I have examined. In the more advanced cases the growth is

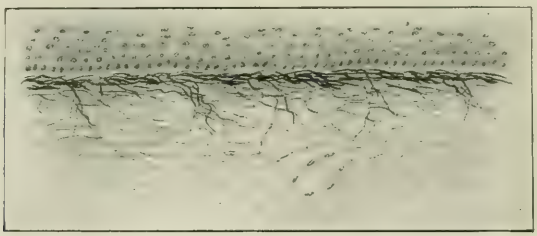


FIG. 12.—The normal epithelium of the vaginal cervix, showing the subepithelial elastic fibre plexus.

so extensive that the signs of pre-existent inflammation are not so obvious, but they are to be found nevertheless if search be made for them.

It is necessary then to describe in detail the pathology of chronic cervicitis, and to study particularly the changes seen in cervical erosion. In the earlier phases of this condition the subepithelial tissue underlying the squamous epithelium is infiltrated with lymphocytes. (Figs. 12 and 13.) The same appearances are seen under the columnar epithelium of the cervical canal higher up and around the mucous glands. In these glands are seen polynuclear leucocytes, probably a remnant of the original acuter inflammation which initiated the process.

The squamous epithelium over the eroded area is largely broken up, lymphocytes have intercalated themselves between

the individual cells, and these latter appear loosened in their attachment to one another, so that the superficial cells have desquamated. The surface is therefore irregular, and the epithelium thinner than normal.

Immediately underlying the squamous epithelium of the normal cervix is a fine plexus of yellow elastic fibres. In the stage of erosion that I am describing this plexus becomes broken up apparently as a result of the lymphocytal proliferation, whilst a new layer of tissue deficient in elastic fibres is formed above it. This proliferation is irregular in its distribution, especially at the periphery of the inflammatory area, and consequently the elastic plexus is at first destroyed irregularly. The whole cervix is unusually vascular, and an abnormal number of thin-walled blood spaces are seen.

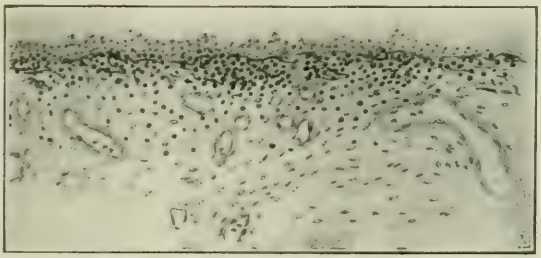


FIG. 13.—Early erosion of the cervix, showing the breaking up of the epithelial layers and the destruction of the elastic fibres coincident with the lymphocytal and plasma cell proliferation.

At a later stage plasma cells begin to appear under the epidermis. They bear the same relation to the lymphocytes and epithelial cells that I have described elsewhere. The elastic plexus now entirely disappears and the loosened epidermal cells become largely detached, so that practically only the basement layer remains, and this is deficient at various points where the exposed highly vascular connective tissue comes to the surface. In cases where the tissue cell proliferation is very profuse, these areas become raised as papillary elevations which consist entirely of plasma cells.

Coincidently with these changes under the epithelium is seen a great hypertrophy of the cervical glands, which become

characteristically convoluted. They lie in a matrix containing a great number of plasma cells and lymphocytes, which are specially aggregated around them. The hyaline tissue cells are also increased in quantity. (Fig. 14.) It is probable that the cellular condition of the subepithelial tissue favours epithelial ingrowth, and that the loss of the elastic tissue also acts in that direction, for in sections where this plexus is irregularly destroyed it is noticeable that protrusions inwards of the epithelium correspond to areas of tissue cell proliferation and disappearance of the elastic fibres. (Fig. 15.)

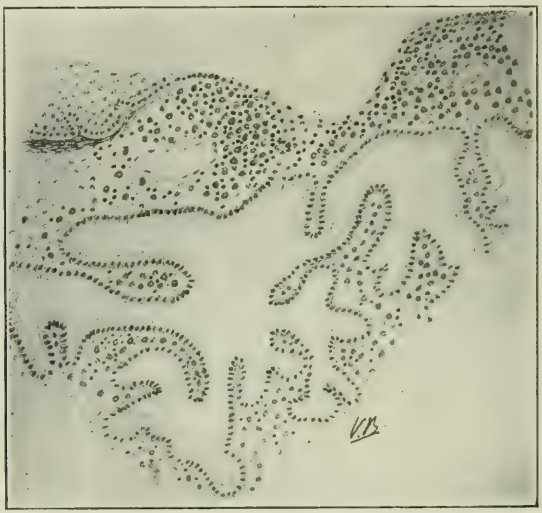


FIG. 14.—Cervical erosion. A later stage, showing hypertrophy of the glands, disappearance of the surface epithelium, and aggregation of plasma cells.

Somewhat later the epithelium overlying the area of the erosion, which at first was thinned and irregular, also hypertrophies, and layer upon layer of squamous cells is laid down which show an abnormal tendency to keratinise. Thus the whole area of the erosion becomes covered by a thickened whitish-looking squamous epithelium exhibiting large interpapillar downgrowths, so that the area which was originally covered partly by squamous and partly by columnar epithelium becomes coated with squamous epithelium alone. The ducts of the glands in this area now have to pass through

many layers of squamous cells to reach the surface. These cells presently block the ducts, and the resulting retention cysts form the so-called ovules of Naboth. The de-elasticised

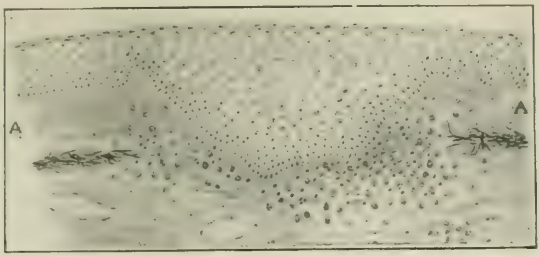


FIG. 15.—Chronic cervicitis, showing ingrowth of epithelium at a spot where the elastic fibres have been destroyed by plasma cell and lymphocytal aggregation. Note the layer of de-elasticised tissue intervening between the epithelium and the elastic fibres at A.

connective tissue still exhibits many lymphocytes and plasma cells specially marked at the tips of the interpapillar epithelial processes and around the glands. (Fig. 16.)

FIG. 16.—A late stage of erosion of the cervix, showing the hypertrophied epithelium, blocked glands, and cellular subepithelial tissue.

In the oldest stages the lymphocytes and plasma cells largely disappear, and the subepithelial tissue presents a fibrous matrix with a number of oval hyaline connective tissue cells contained in it.

Carcinoma of the cervix may begin either in the thickened squamous epithelium that covers the area of an old erosion or in the hypertrophic cervical glands higher up. In either case the development of malignancy appears to bear some relation to the altered conditions that obtain between the epithelium and its underlying connective tissue as a result of long continued cervicitis.

In squamous cell carcinoma the epithelial downgrowths correspond to the large interpapillary epithelial processes that characterise the old erosion. Surrounding them are very large masses of plasma cells together with many lymphocytes. The hyaline fixed tissue cells do not show much evidence of

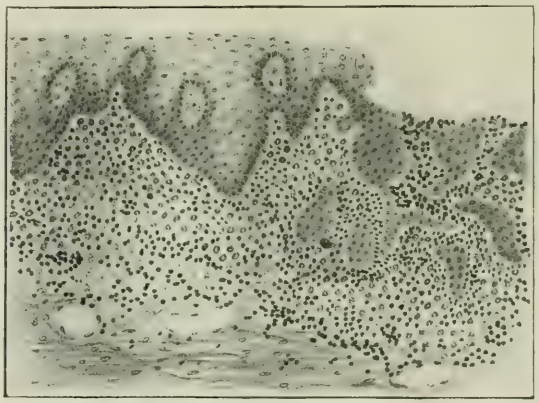


FIG. 17.—Edge of a squamous-celled carcinoma of the cervix, showing the precarcinomatous state of the area not yet malignant.

proliferation. The superficial muscular and fibrous elements are rarefied and largely destroyed by the plasma cell proliferation, and the epithelial invasion is diffuse. Underlying the thickened epithelium beyond the margin of the actual growth the same tissue changes are seen in progress, and the subepithelial elastic plexus is absent. (Fig. 17.)

In the columnar cell growth similar tissue changes are observed. The malignant glands are invading a tissue rich in plasma cells and lymphocytes. Beyond the area of actual malignancy many hypertrophied glands are seen surrounded by masses of plasma cells. The squamous surface of the cervix shows changes due to old inflammation.

In the case of either form of growth, then, the tissue changes are those of a chronic cervicitis which has undoubtedly preceded the onset of malignancy.

Carcinoma of the Skin.

There are a number of conditions which clinically predispose to carcinoma of the skin. It is necessary to consider these conditions separately, and I shall proceed to describe the result of my own observations in this connection.

Scar Tissue.—If a healthy and united wound be examined on the third day after its infliction remarkably little is to be seen. The line of the incision is distinguished by a slight irregularity of the epidermis and by the abrupt break in the elastic fibres. Here and there in the deeper parts are seen collections of fibrin and entangled blood corpuscles. The tissues bounding the wound show very little increase in cellularity. Such as there is is due to large connective tissue cells with hyaline nuclei. These cells are also found entangled in the collections of fibrin.

On the sixth day an increased number of large tissue cells are seen, and in addition some lymphocytes make their appearance. The elastic tissue appears to have retracted from the wound margins, so that when stained by Weigert's method a definite de-elasticised streak of tissue appears. Further, the margins are thickened by a material resembling collagen, but staining faintly with methyl violet.

On the tenth day there is very little further change. The fibrin deposits have disappeared, and the tissues are entirely united across the wound, with the exception of the elastic fibres, which are absent over this area.

On the twenty-second day the disappearance of the elastic tissue for some distance around the wound is very marked. Large mononuclear hyaline tissue cells are seen proliferating in groups, and a number of new thin-walled blood spaces have formed. Lymphocytes are seen in and around these spaces.

On the fortieth day the scar is definitely raised. Stained by Weigert's method it is seen that elastic tissue is entirely absent over a large and somewhat wedge-shaped area. In this area are many groups of large hyaline connective tissue

cells with a single round or oval nucleus. Besides these there are many lymphocytes, and here and there are occasional plasma cells. The epithelium covering this area is somewhat thinned.

At the end of four months much the same condition is apparent, but there are fewer cells to be seen, and the scar is beginning to contract.

At the end of a year the scar is depressed. Elastic fibres are absent over a large area. The hypercellularity has almost disappeared, and the connective tissue is practically normal in appearance. When stained by Weigert's method, however, the scar area shows up in the section as a pale de-elasticised patch.

In scars the seat of chronic irritation, however, a different appearance obtains. The connective tissue is rich in a number of cell types consisting of lymphocytes, plasma cells, and hyaline tissue cells, arranged in a manner practically identical with that seen in the other chronic inflammatory processes I have described. The epithelium covering these irritated scars is at first thin and ill-formed; at a later period, however, it becomes hypertrophied and thickened. Elastic tissue is absent as in the healthy scar.

Chronic Suppurating Ulcers.—The granulations forming the free surface of a chronically suppurating ulcer or sinus are microscopically composed of a number of hyaline cells with pale oval nuclei and united to one another by delicate processes. These cells stain very poorly, and their appearance suggests a low vitality.

Intermixed with them are numbers of polynuclear leucocytes so massed at the actual free edge as almost to obscure the paler connective tissue cells. As one passes deeper into the tissues the polynuclear leucocytes decrease and the hyaline tissue cells become more defined. Lymphocytes begin to make their appearance to the exclusion of the polynuclear leucocytes, and deeper in still plasma cells are seen in increasing numbers. As the periphery of the process is approached polynuclear leucocytes disappear altogether from the field of view, and the dense cell aggregations consist entirely of lymphocytes and plasma cells lying in a groundwork of hyaline fixed con-

nective tissue cells. Elastic tissue is totally absent from the whole area under consideration.

At the edge of the ulcer the epithelium is undermined for a considerable distance by this connective tissue cell proliferation, and the normal subepithelial elastin is absent. Moreover, the epithelium is greatly hypertrophied, and exhibits long and often slightly branched interpapillar processes. Thus both in chronically irritated scars and at the edge of very chronic ulcers a similar condition is eventually arrived at, namely, a much hypertrophied epidermis superposed on a connective tissue exhibiting a characteristic cell proliferation and a total deficiency of elastic tissue.

Chronic Warty Conditions.—A certain proportion of carcinomata of the skin begin on a previously warty condition which has existed for some time before the onset of malignant disease.

A histological examination of such a specimen exhibits the structure of typical squamous cell carcinoma, but in the outlying portion, not as yet malignant, the epithelium is greatly thickened, the interpapillary processes are long and branched, and there is a corresponding elongation of the papillæ themselves. The subepithelial connective tissue is hypertrophied and unusually dense owing to a great increase in the white fibrous elements. Here and there in this tissue are seen aggregations of lymphocytes and plasma cells, whilst the hyaline connective tissue cells are increased in number.

In sections of this warty skin stained by Weigert's method it is seen that the tissues underlying the epidermis for a considerable extent present a complete absence of the elastic tissue which should normally occur there, and microscopically therefore the condition is identical with that of the other pathological states clinically predisposing to carcinoma.

Lupus Vulgaris.—The frequency with which carcinoma supervenes on old lupus is known. This has been especially frequent since the introduction of X-ray Treatment.

An acute tubercular lesion of the skin is not characterised by the presence of plasma cell and lymphocytes, the nodules being made up almost entirely of hyaline endotheliod cells from which the giant cells appear to be a derivative.

In old-standing cases, however, the hyaline tissue cells disappear before an increasingly large quantity of plasma cells and lymphocytes, and the condition of the subepithelial tissue becomes cytologically identical with that of the other precarcinomatous conditions that have been considered. The elastic elements have early disappeared. Finally comes an epithelial hypertrophy on which carcinomatous growth may be superimposed.

Rodent Ulcer.—Borrmann found evidence of pre-existent tissue changes in every specimen of the very large number of cutaneous carcinomata examined by him.

In the specimens of rodent ulcer studied by me I have also found these changes. They consist in a disappearance of the

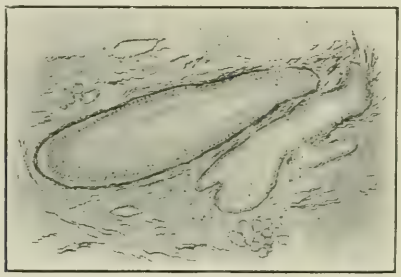


FIG. 18.—A normal hair bulb and sebaceous gland, showing the distribution of the elastic tissue. Weigert's stain.

delicate elastic fibres which normally encapsule the hair follicles and sebaceous glands (Fig. 18), and the substitution of a hyaline connective tissue in that situation. There is a similar change in the constitution of the connective tissue immediately adjoining the surface epithelium, but beneath this zone is found an abnormal quantity of granular elastin, certainly the product of chronic irritation.

The connective tissue remote from the actual seat of malignancy exhibits an abnormal number of lymphocytes, whilst local areas of plasma cell proliferation are seen, chiefly around the hair follicles.

Moreover the subepithelial tissue is hyperæmic, and the epithelial elements, especially those of the sebaceous glands, are hypertrophied. (Fig. 19.)

X-ray Carcinoma.—Rowntree, in an investigation published in the present volume of the Archives of the Middlesex Hospital, has found that in the skin exposed to X-rays there is an initial hypertrophy of the epithelial elements followed by an atrophy with complete disappearance of the hair bulbs and sebaceous glands.

The connective tissue shows changes which particularly affect the elastin. In an advanced case of X-ray dermatitis this has completely disappeared in a zone immediately under the epithelium and is replaced by an immature connective tissue. In cases where carcinoma is threatening to supervene large numbers of plasma cells and lymphocytes are present.

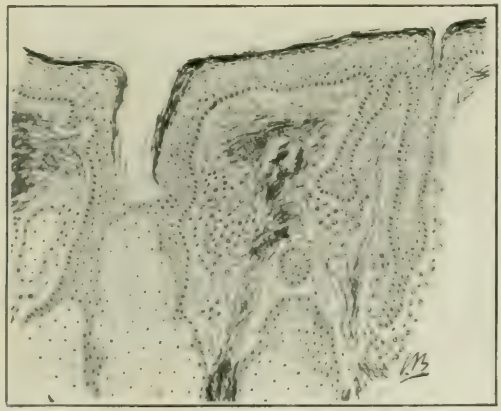


FIG. 12. Tissues beyond the edge of a rodent ulcer, showing disappearance of elastic tissue around the hair-bulbs and under the epidermis, with an increased amount in the tissues elsewhere. Weigert's stain.

Carcinoma of the Breast.

In the case of carcinoma affecting the breast the existence of an antecedent inflammatory state is not clinically so obvious as in the case of carcinoma affecting vulva, tongue, cervix, and skin.

From the pathological standpoint also evidence of prior change in the breast tissue is much more difficult to prove. The cause of this is that histologically the breast is an extremely variable organ, and that therefore it is very difficult to set a standard of normality with which to compare its

pathological changes. I would therefore recall some points in connection with its normal histology. (Fig. 20.)

The ultimate acini of the breast are rounded in form and are lined with a single layer of broadly columnar or polyhedral epithelium. These acini occur in groups embedded in the mammary matrix. This matrix is a peculiar tissue made of a very fine framework of fibroglia fibres on and around which appears to be deposited a soft homogeneous collagenous-looking substance which on heating can be shown to contain a considerable proportion of fat. There are comparatively few cells to be seen in this matrix except in the immediate vicinity of the acini and ducts. These cells are of two

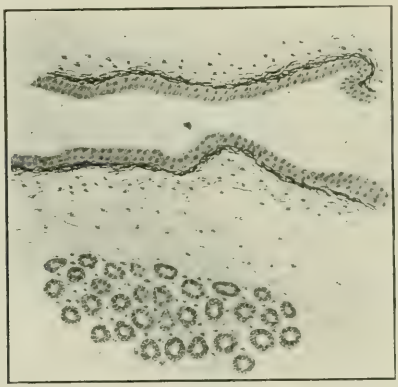


FIG. 20.—Portion of a lactating breast, showing a part of a duct and a group of acini. The distribution of the elastic fibres immediately under the epithelium of the duct is well shown.

varieties—(1) hyaline connective tissue cells with a reticular-looking nucleus, and (2) mast cells. The hyaline cells are particularly aggregated around the groups of acini, and form a loose cellular sheath to the ducts. The mast cells are single and are scattered irregularly through the matrix. The ducts themselves are lined by a single layer of short columnar epithelium. The distribution of the elastic tissue in the breast is of much importance. Each duct is invested by a definite elastic layer situated almost immediately under the epithelium and intervening between it and the layer of hyaline connective tissue cells. This elastic tunic is prolonged to the finest ducts, but ceases where they pass into the acini.

In the larger blood vessels an elastica is present as usual, but in the matrix elsewhere there is a striking absence of this tissue, particularly in the young breast.

The above general type, however, presents many varieties. Thus in the lactating breast the number of acini is very large, their epithelium is swollen, and the number of connective tissue cells surrounding them is increased. The ducts partake of the same hypertrophy. In the poorly developed or young virgin breast the parenchyma is scanty. The acini are small, their circular form and lumen are not well developed, and whilst the larger ducts are formed, many of the smaller ones are represented by mere rows of compressed cells without a definite lumen. In well-developed but non-lactating mammæ an intermediate condition is seen.

The only constant age-change appears to be a tendency for the amount of elastic tissue to increase with advancing years, whilst the matrix becomes less homogeneous in appearance.

The Changes of Chronic Mastitis.—In the early stages of chronic mastitis there is marked evidence of increased cellularity. The number of acini is much augmented, whilst individually they show a hypertrophic condition of the epithelial lining. The mammary matrix surrounding the groups of acini exhibits an unusual number of hyaline tissue cells, amongst which are found scattered lymphocytes and plasma cells.

The ducts are enlarged and their epithelium hypertrophic, so that irregular projections may be formed which protrude into the lumen. The mammary matrix in proximity to the ducts shows marked cell proliferation, both lymphocytes and plasma cells being present. I have closely examined tissue from a number of breasts of different ages, and have found that plasma cells are absent from the normal organ.

Coincidently with this cell proliferation changes in the distribution of the elastic tissue are seen; and whereas in the normal organ the epithelium practically rests on the elastica, a hyaline layer of tissue now intervenes between the epithelium and the elastic fibres.

In more advanced cases the elastic tissue of the smaller ducts becomes irregular and finally disappears, whilst the

groups of acini become surrounded by an island-like area of wavy fibrous tissue quite different in appearance from the mammary matrix beyond them. (Fig. 21.)

Carcinoma of the Breast.—An examination of a large number of specimens shows that the growth of carcinoma of the breast is at first pluricentric; that is to say, there occurs a progressive conversion of non-malignant epithelium into carcinoma cells. In early specimens gradations of form between the tubules and acini outside the growth and the alveoli of the growth itself have been found by Leitch, as described in the present report of the Department, and my

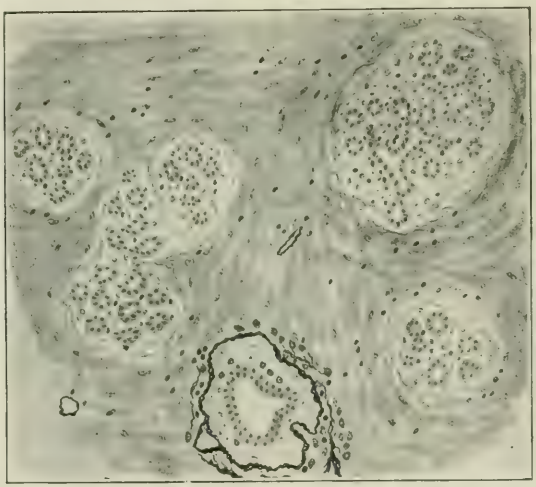


FIG. 21.—Chronic mastitis, showing the altered relation of the elastica to the epithelium of the duct and the new fibrous tissue surrounding the groups of acini.

work confirms his. In more advanced cases such changes are not apparent, because practically all the breast tissue proper is destroyed.

The tissue cell proliferation in carcinoma of the breast presents characteristics identical with those of carcinoma in other sites. It is most marked at and beyond the periphery of the growth. Lymphocytes and plasma cells are the chief cell forms, but they are not present as a rule in the dense aggregations seen in squamous cell carcinoma, nor is the existence of definite zones characterised by different cell types

so obvious. That this is so is, however, to be expected when one considers that instead of the malignant growth taking place from a plane surface it does so from one already extensively convoluted. Thus is accounted for those appearances of ducts or alveoli undergrowing early malignant change lying amongst well-formed carcinomatous alveoli which have evidently taken some time to produce. As a result of this plasma cell and lymphocytal proliferation the mammary matrix becomes rarefied and the homogeneous ground-substance disappears.

In the older part of the stroma the number of cells is progressively reduced, and in the oldest parts only the hyaline tissue cell remains, together with many fibroglia fibres on and around which a collagenous ground-substance is apparently deposited. Beyond the periphery of the growth new lymph nodes are occasionally encountered with well-marked germinal areas surrounded by plasma cells. Elastic tissue is for the most part absent from the stroma. One must, however, remember that the normal breast matrix contains very few of these fibres.

Their disappearance in chief part undoubtedly accompanies the connective tissue cell proliferation. For the rest certain of them which escape the results of the proliferation and become isolated in the stroma appear to undergo a simple atrophy.

In certain cases, however, isolated areas are scattered through the stroma containing a very large amount of a granular-looking elastin. Part of this may be due to condensation of pre-existing fibres, but some of it is undoubtedly newly formed. This formation and condensation invariably occurs around one of the larger ducts which has as yet escaped destruction by the growth.

Hence it would appear that the stroma of a mammary carcinoma is essentially that of the breast itself, with the addition of certain elements as a result of the carcinomatous process.

The relation between Mastitis and Carcinoma of the Breast.—From the clinical standpoint a certain number of cases of carcinoma of the breast appear to have been

definitely preceded by mastitis, but in the majority neither sign nor history of such condition is obtainable. The evidence of pre-existent inflammatory change is much stronger, however, from the histological standpoint. In the course of my investigation I have succeeded in finding traces of mastitis in all early cases. The ducts outside the carcinomatous area exhibit the same layer of hyaline tissue between the epithelium and the elastica that occurs in chronic mastitis, and surrounding them are found lymphocytes and plasma cells. The groups of acini outside the carcinoma in some of my specimens are typical of mastitis, but in others show no definite change. (Fig. 22.) It is,

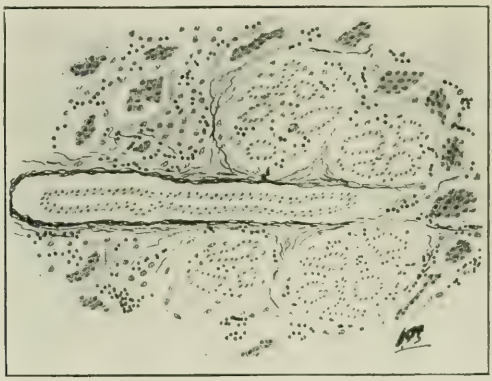


FIG. 22.—Groups of mammary acini and a duct showing the changes of chronic mastitis and surrounded by carcinoma.

however, to be remembered that the changes due to mastitis are commonly localised in multiple small areas, and where the breast tissue has been extensively destroyed by the growth evidence of these changes may be absent from that which remains, for carcinoma starting in a localised area of mastitis would soon obliterate all traces of the pre-existent inflammation. This is at least a possible explanation of cases of carcinoma from which evidence of old mastitis is histologically absent.

Carcinoma of the Intestine.

In the tissue around a carcinoma of the rectum (histologically a typical columnar cell carcinoma) which formed

an ulcer in the posterior wall of the gut less than a centimetre square in extent the following appearances were found. (Fig. 23.)

At the edge of the growth are seen those appearances described by Ribbert, viz., a great elongation of the gland tubules balanced by an equal upgrowth of interglandular connective tissue. The tips of the gland tubules bear a normal relation to the muscularis mucosa, suggesting that the primary change was an overgrowth of the connective tissue to which the glandular elongation was secondary. The transition from this area to that of actual malignancy is abrupt.

The stroma of the growth is scanty and fibrous—at its

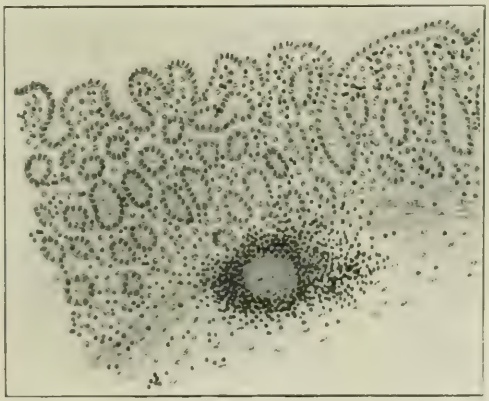


FIG. 23. Tissues beyond the edge of a carcinoma of the rectum, showing hypertrophied glands, plasma cell proliferation, and loss of elastic tissue, together with an abnormal lymph node.

periphery particularly are seen many lymphocytes and plasma cells. Beyond the growth in *either direction* the interglandular connective tissue of the mucosa is crowded by plasma cells, with an abnormal number of lymphocytes. This plasma cell proliferation extends for a distance beyond the growth greater than the diameter of the ulcer itself. All the solitary follicles show hypertrophy and large germinal areas with many mitotic figures. No polynuclear leucocytes are seen.

When stained by Weigert's method it is seen that the plexus of elastic fibres, which normally forms a well-marked

stratum in the connective tissue beneath the gland tubules, is entirely absent in the area of the plasma cell proliferation. It is absent also in the more superficial portions of the stroma, but a good many fibres remain in its deeper part. This disappearance of elastic tissue, together with a dense plasma cell infiltration of the subepithelial tissue far beyond the area of the growth, is very significant. Had it occurred on the proximal side only it might have been suggested that it was due to a stercoral proctitis such as commonly occurs above a carcinomatous stricture of the rectum. Apart from the fact that the growth was too small to cause any stricture, this idea is negatived by its presence on the distal side of the ulcer and by the absence of polynuclear leucocytes. The appearance suggests strongly that the growth itself began on a surface already the seat of marked inflammatory changes.

Two other early cases that I have examined lead me to the same conclusion—namely, that carcinoma of the rectum starts in an area of chronic proctitis. Advanced growths are useless for the investigation of this point, firstly because the extensive spread of the carcinoma destroys the entire precarcinomatous area, and secondly because of the secondary inflammatory changes that are superimposed on it.

Carcinoma of the Œsophagus.

In a carcinoma of the œsophagus of small extent the following features were recognised: The tumour is evidently due to the downgrowth at many points of the surface epithelium. Surrounding the down-growing epithelial processes are large masses of lymphocytes and plasma cells arranged in the manner which has been described. Fixed tissue cell proliferation has not occurred to any extent, nor are many polynuclear leucocytes present. In the tissues *both above and below the growth*, and extending over an area at least double that of the carcinomatous growth, is a plasma cell proliferation together with many lymphocytes. The epithelium over these portions of the œsophageal wall is thickened irregularly.

Stained by Weigert's method it is seen that the normal lamina of elastic fibres which underlies the epithelium is

absent, not only near the growth or in the region of the plasma cell proliferation, but beyond this also where no inflammatory cells are present. As I have pointed out, absence of elastic tissue in positions where it is normally found, and unassociated with a present tissue cell proliferation, is a certain sign of old inflammatory change. The fact that indications of this change are present on both sides of the growth is as important as in the analogous condition of the rectum. The general appearances suggest then that in this case the growth was superposed on a chronic œsophagitis, and this conclusion is supported by examination of other specimens.

THE CONNECTIVE TISSUE IN RELATION TO ADVANCED EXTENSIONS OF PRIMARY CARCINOMA.

It has been shown that relatively the connective tissue cell proliferation is extensive in early carcinoma, and that the tissues in which the growth is taking place are the seat of marked pre-existent changes.

At the periphery of an advanced growth, however, the tissues that surround it not only show no changes of pre-

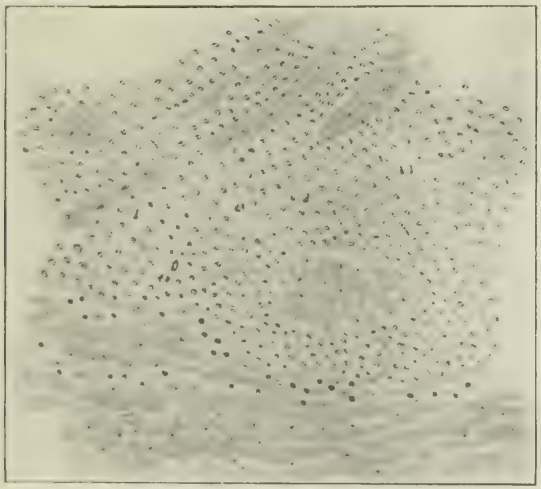


FIG. 21.—Advanced extension of carcinoma of the tongue amongst muscle bundles, showing passivity of the surrounding tissues.

existent inflammation, but exhibit little or no tissue cell proliferation. They appear to be simply pressed aside by the tumour cells, and whilst the cellular elements, specialised structures, and elastic fibres undergo atrophy, the white fibres become condensed or even augmented by an increased deposit of collagen.

These changes are well seen in specimens of carcinoma of the tongue invading the deeper musculature of the organ, in advanced carcinoma of the cervix, and in extensive mammary growths. (Fig. 24.)

This change in the behaviour of the connective tissues which characterises advanced extensions of the growth is associated with a different manner of epithelial invasion, so that instead of the diffuse and irregularly concentric spread which is typical of the early primary tumour, a regular progression obtains which is restricted along certain lines of presumably least resistance.

The Connective Tissue in Relation to Permeated Lymphatics.

The investigations of Sampson Handley, carried out in the Laboratories of the Middlesex Hospital Cancer Investigation Department, have demonstrated that the majority of metastatic nodules in the case of the breast are to be regarded as terminal outcrops of long lines of continuous lymphatic permeation. He also noted that the "healthy" carcinoma cells seen in the lymphatics at the extreme microscopic growing edge appear to excite no tissue re-action either in the lymphatic wall or outside it, and he states that "according to my observations the living cancer cell in its most active state, not degenerate from pressure or any other cause, exerts no attractive influence on the leucocytes." But he found that where the carcinoma cells had degenerated a process of perilymphatic fibrosis associated with lymphocytal aggregation occurred, which terminated in the destruction of the moribund tumour cells and the obliteration of the lymphatic channel. Thus it would appear that a mass of carcinoma cells when dead or dying excites in the tissues around it a reaction similar to that produced by other foreign

bodies, but whilst living and active it produces no such reaction.

My own investigations support Handley's findings. There is a remarkable absence of any tissue reaction in the wall of a permeated lymphatic so long as the tumour cells contained within it exhibit no degenerative changes. (Fig. 25.) As the lymphatic distends the perilymphatic tissues undergo some condensation, and where a number of these are in close proximity this condensed tissue forms a stroma around their cross sections.

Near the primary growth this thickening of the lymphatic wall is so pronounced as to suggest a new deposit of collagen

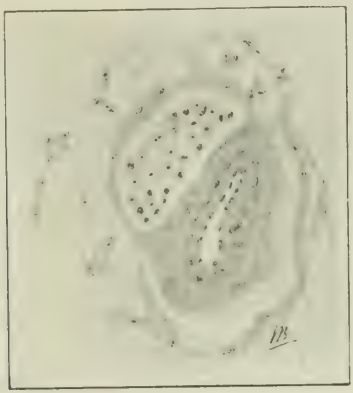


FIG. 25.—Carcinoma cells from a mammary growth lying in a lymphatic by the side of a small blood vessel. The tissues of the lymphatic wall show no change.

there, for I have found no evidence of a preliminary fixed tissue cell proliferation to account for it. Elastic fibres occurring in the perilymphatic tissue are at first not altered, but with the thickening of the lymphatic wall they atrophy and disappear. I have further found no evidence of any changes in the walls of the lymphatics prior to their invasion by the carcinoma cells, but along lymphatic tracks already the seat of permeation an abnormal number of lymphocytes are seen in the lymph channels. This may be ascribed, first, to the retirement of lymphocytes before the invading tumour cells, and, secondly, to carcinomatous obstruction of the lymph vessels.

The Connective Tissue in Relation to Metastatic Nodules.

These nodules exhibit microscopic appearances in strong contrast to those of the primary growth. Thus they tend to be spherical, to be sharply circumscribed, and to be movable when the tissues in which they are growing permit of it. A primary carcinoma of the breast and a subcutaneous nodule secondary to it are good examples of these differences.

The impression that these different macroscopic appearances indicate a different method of growth is confirmed by microscopic examination of metastases from various parts.

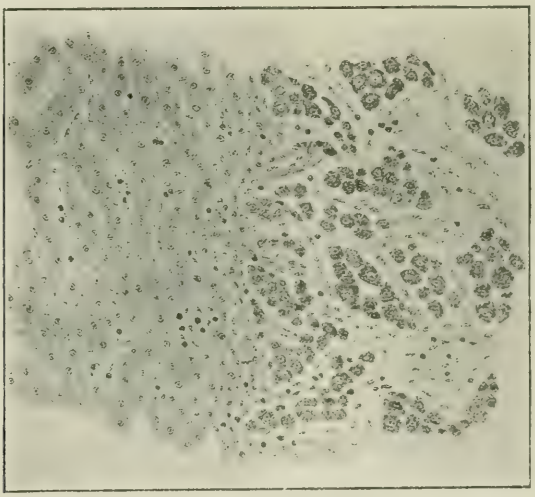


FIG. 26.—The edge of a hepatic metastasis from a case of primary mammary growth, showing the passivity of the invaded tissues.

Hepatic Metastases.—The sharp edge of a hepatic metastasis shows an abrupt transition from the liver cells to those of the new growth. The only changes recognisable in this area are a compression and subsequent atrophy of the liver cells, together with a moderate accumulation of lymphocytes. There is no evidence of these cells having been produced locally, and their number is consistent with the suggestion that they have been expelled from the area of the metastasis by the cells of the new growth. Plasma cells are absent, and there is little or no evidence of proliferation of the fixed tissue cells. (Fig. 26.) The stroma of the growth is densest in

its central portions, and is very acellular. It appears to be formed of the pre-existent connective tissue of the liver condensed and further augmented by collagenous deposit. Elastic tissue is absent from it, but the normal liver only shows these fibres in its larger areas of connective tissue. The general impression derived from a study of these growths is that the tumour cells are spreading into the liver tissue by a radial expansion between its fixed tissue elements, whilst the cells of the hepatic parenchyma suffer displacement and atrophy.

Renal Metastases.—The appearances of early metastases in

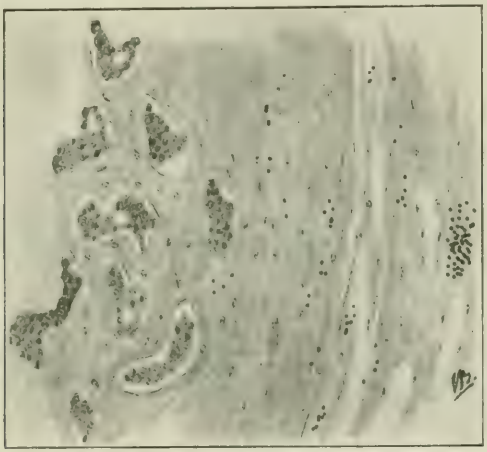


FIG. 27.—Edge of a subcutaneous metastasis from a case of mammary carcinoma, showing the passivity of the surrounding tissue.

the kidney are, *mutatis mutandis*, similar in all respects to those met with in the case of the liver.

Subcutaneous Nodules.—The circumscription of the subcutaneous nodule is very marked, and the tissues up to its very edge are normal. The nodule itself consists of a number of carcinomatous alveoli lying in a dense fibrous matrix containing much collagen. This matrix exhibits very few cells. Those seen are mostly of the fixed tissue cell type, together with a certain number of lymphocytes, but no plasma cells are apparent. The matrix frequently extends beyond the limits of the outermost cells of the growth. This zone when present corresponds to the area of flattened liver

cells seen in hepatic metastases and formed by the compression and condensation of the surrounding normal tissues. Elastic tissue is seen at the periphery of the nodule, but is absent from the central parts. The acellularity of the whole process, as far as the connective tissues are concerned, is very marked. (Fig. 27.)

Carcinoma en Cuirasse.—This form of carcinomatous growth may be regarded as an intermediate condition between a primary growth and a secondary metastatic nodule. We have seen that in the deepest parts of an advanced primary growth the inactivity of the connective tissue which characterises metastases is already apparent. In carcinoma en cuirasse this passiveness of the invaded connective tissue is well seen. The cells of the new growth are insinuating themselves diffusely into the meshes of the normal subcutaneous connective tissue. The tissues themselves are pressed aside and condensed, whilst the elastic fibres undergo atrophy. At the periphery of the process a certain number of lymphocytes is aggregated, and small collections of them are also seen within the area of the growth, but there is no formation of plasma cells or proliferation of the fixed tissue cells. On the contrary, these latter atrophy and disappear, so that in the older parts of the infiltrated area the stroma is acellular. Here large areas are seen in which the carcinoma cells are degenerate.

Metastatic Mammary Carcinoma of the Opposite Breast.—It might be suggested that the differences in the connective tissues manifested in primary and secondary carcinoma respectively were due to the different sites in which they were growing, and not to any inherent difference in the processes constituting the economy of the growths. Such a suggestion is, however, negatived by examination of metastatic carcinoma of one breast secondary to a primary growth in the opposite organ. Here, as in the other examples of secondary nodules that I have cited, the connective tissues exhibit no active changes. A moderate number of lymphocytes are found in and beyond the stroma, but a tissue cell proliferation comparable with that seen in the primary growth is not present.

The Changes in Lymphatic Glands in connection with Carcinoma.

I have thus far reserved a consideration of the changes seen in lymphatic glands in connection with carcinoma, because they differ in some important respects from those seen in the other areas of secondary carcinomatous invasion that I have mentioned. The enlargement of the lymphatic glands in a carcinomatous area begins before any of the cells of the growth have reached them.

Microscopically, this precarcinomatous enlargement is due to three factors: (1) The appearance of large germinal areas in the gland whose cells exhibit many mitoses. (2) A great increase in the number of lymphocytes in the individual

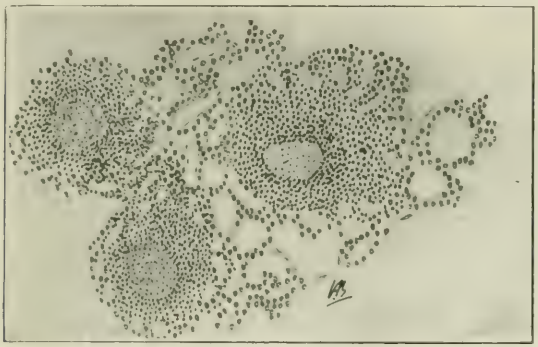


FIG. 28.—Precarcinomatous enlargement of a lymphatic gland, showing hypertrophied follicles, large germinal areas, and diffuse plasma cell proliferation.

follicles; this increase is presumably chiefly due to the production of lymphocytes by the cells of the germinal areas; but, as I have already suggested, it may in part depend upon their expulsion from situations already the seat of carcinomatous invasion. (3) The appearance of plasma cells in large quantities in the stroma and capsule of the gland. When the number of these cells is very large they extend into the peri-adenoid tissue. There is no increase in the hyaline tissue cells that normally occur in the stroma. (Fig. 28.)

It is thus apparent that the precarcinomatous lymphatic gland exhibits the same cytological appearances as characterise the inflammatory proliferation going on around the

early primary growth. The suggestion that these changes are due to bacterial absorption from an ulcerating primary growth is negatived by their occurring equally in non-ulcerated carcinoma of the breast. I have not obtained sufficient material from cases of precarcinomatous inflammation to conclusively study the effect of these states on the neighbouring lymphatic glands. Clinically the glands are often somewhat enlarged in these conditions, and pathologically it has been demonstrated that new lymph nodes surrounded by plasma cells are frequently seen in regions of leukoplakic inflammation. I have investigated ten specimens of axillary glands removed together with the breast which were proved microscopically to be the seat of mastitis alone, and all these show abnormally large germinal areas, and some increase in the gland stroma with a certain number of plasma cells therein, and thus afford evidence of an early condition of that change met with in lymphatic glands in connection with carcinoma, and are an argument that the changes are produced by the antecedent inflammation and not by the carcinoma itself.

The invasion of lymphatic glands by carcinoma cells takes place from the centre outwards. The lymphocytes are evidently subjected to compression, and surround the growth in closely-packed concentric rows. There is no evidence of their destruction by the carcinoma cells, and they appear to be simply expelled from the gland so that in the later stages they are only seen in considerable numbers immediately under the capsule. A certain number, however, are seen in the stroma of the growth. This stroma is as a rule scanty, and appears to consist of the original reticulum of the gland together with many plasma cells, which, on account of their fixity in the tissues, are unable to retire before the advancing epithelial cells. In the older part of the stroma the plasma cells, together with its other cellular constituents, atrophy, whilst the fibrous elements become compressed and denser.

The Question of the Specificity of the Connective Tissue Changes which Precede and Accompany Carcinoma.

The question of absolute specificity in regard to the tissue changes accompanying carcinoma is at once negatived, because

it has been shown that identical histological appearances characterise those inflammatory conditions which appear to always precede the occurrence of epithelial ingrowth. The inquiry is thus reduced to a comparison of the connective tissues in carcinoma and precarcinomatous states with other forms of inflammation.

Acute Suppurative Inflammation.—The condition of the connective tissues in acute suppurative inflammation bears no likeness to that seen in the states we are investigating. Polynuclear leucocytes are the conspicuous objects of the microscopic field. The fixed connective tissues are pressed aside by their aggregations, and are in a condition of acute degeneration, or actual necrosis, whilst epithelial cells involved in the process share the same fate.

Chronic Suppurative Inflammation.—In the earlier phases of chronic suppurative inflammation the connective tissue changes bear no likeness to those in the carcinomatous states, polynuclear leucocytes and hyaline tissue cells being alone present, whilst epithelial growth is inhibited. At the periphery, however, of an area of chronic suppuration, where presumably the intensity of the irritant is not so great, and over the whole area when the inflammation has subsided in intensity and pus formation has ceased, a type of chronic proliferative inflammation is developed, characterised by lymphocytes, plasma cells, fibrillar changes, and epithelial hypertrophy, on which malignancy is frequently superposed, e.g., carcinoma developing upon chronically inflamed scars and old ulcers.

Tuberculous Inflammation.—The specific reaction of the connective tissue to the tubercle bacillus is very characteristic, and does not in the least resemble the inflammatory states which precede carcinoma or accompany it. An acute tuberculous lesion is formed by proliferation of the hyaline fixed tissue cells, which play but little part in the carcinomatous states, whilst the giant cells found in this condition are conspicuously absent in carcinoma. Lymphocytes are sparsely present at the edge of an early nodule, and plasma cells are only occasionally seen.

In some special forms of chronic tuberculous inflammation, however, such as old-standing lupus, the hyaline endothelioid cells are few, lymphocytes are increased in number, and plasma cells make their appearance in large quantities, whilst the elastic tissue has previously disappeared. Moreover in these secondary conditions the vascularity of the diseased area is increased, and epithelial overgrowth occurs. It is on such an area that carcinoma may subsequently develop.

Syphilitic Inflammation.—The cytological appearances of the connective tissue in a primary chancre resemble those seen in the carcinomatous states much more closely than is the case in an acute tuberculous lesion. Thus, from an early period, plasma cells and lymphocytes are conspicuous objects. On the other hand there is a very much greater degree of hyaline fixed tissue cell proliferation. Moreover the intensity of the irritant is such that epithelial proliferation is inhibited, and though abnormally long and narrow epithelial processes are seen at the margin of the inflamed area, yet the picture suggests an invasion of the epithelial cells by the connective tissue elements, and not vice versa. Many polynuclear leucocytes are also present.

In acute secondary lesions some plasma cells and many lymphocytes are seen, but there are also great numbers of polynuclear leucocytes; and all the cells in the inflammatory area are tending towards necrosis. In long-continued inflammation of syphilitic origin these appearances give place to those that are typified in chronic superficial glossitis.

Summary.

To summarise, then, we see that the connective tissue changes associated with established carcinoma are identical with those met with in precarcinomatous states. And, moreover, we see that these precarcinomatous states can be attained by many different routes, starting in inflammatory conditions which histologically are at first quite distinct from one another, and which are initially due to entirely different forms of irritant.

This fact is of great interest, because logically one would expect that each form of irritant would lead to its own

peculiar form of tissue reaction, and within limits experimental research supports such a view. In short, it is conceivable that the immediate agent of the precarcinomatous states may be identical in them all, although the initial changes in the tissues were due to totally different causes.

The Structure of the Stroma in Carcinoma.

The elements of the stroma may be divided into (1) those that were pre-existent, and (2) those that are newly-formed.

1. **Pre-existent elements.**—The pre-existent elements consist chiefly of hyaline fixed tissue cells together with their fibroglia processes,

These cells do not appear to be destroyed by the plasma cell and lymphocytal proliferation that is taking place at the margin of the primary growth, for they may be seen lying unaltered amongst them, and occasionally exhibit mitoses.

As the epithelial masses advance they are pushed aside and compressed, and in the older portions of the stroma the cellular elements tend to atrophy, the fibroglia fibres alone remaining. There is, however, no evidence of their actual destruction by the carcinoma cell.

In the more peripheral parts of the stroma pre-existent elements other than the fixed tissue cells occur. Thus certain elastic fibres which have escaped destruction by the plasma cell and lymphocytal proliferation may be seen together with isolated muscle fibres or parenchyma cells, all of which, however, atrophy and disappear, whilst the hyaline fixed tissue cell is still intact.

In advanced tumours of rapid growth the stroma in the central areas is entirely acellular and appears to be undergoing degenerative changes coincidently with the epithelial cells.

2. **New-formed elements.**—Where a marked plasma cell proliferation has preceded the growth, as at the primary site and in lymphatic metastases, these cells form part of the stroma. Subsequent to their inclusion in it they lose their characteristic shape and staining reactions and become compressed, elongated, and increasingly hyaline in appearance, whilst in the oldest parts of the stroma they atrophy and disappear altogether. A certain number of lymphocytes also remain in

the stroma to a late period. There is very little proliferation, however, of the hyaline fixed tissue cells, but occasional mitoses both in them and endothelial cells are observed. Besides these new cell elements it has been shown that under certain circumstances local deposits of elastin take place, and, further, that much of the density of the central portions of the stroma is probably due to a new deposit of collagen in or around the fibroglia fibres of the tissue cells.

It would, however, appear that the elements of new formation are usually more than compensated for by the expulsion of all mobile cells from the tumour area and the destruction and absorption of collagen, elastin, and parenchymatous elements which are going on at the margin of the growth, so that in most cases the bulk of the stroma does not equal that of the tissues that originally occupied the area of the growth.

On the Nature and Significance of the Connective Tissue Changes in Relation to Carcinoma.

Finally, it is necessary to pass to a general consideration of the nature and significance of the connective tissue changes in relation to carcinoma in the light of the results of this investigation.

It has already been shown that the carcinoma cell does not act as a *specific* irritant, and, further, there is reason to believe that it does not act as a tissue excitant at all *per se*. For, as has been demonstrated in advanced extensions of a primary growth, the tumour cells penetrate beyond the area of the tissue cell proliferation and lie between the tissue elements without exciting in them any reaction whatsoever. This passivity is still more marked in the tissues surrounding permeated lymphatics, whilst in metastases the invaded connective tissue is equally inactive. The difference that obtains in invaded lymphatic glands is apparent only, since they are already the seat of a precarcinomatous change. The suggestion that the carcinoma cell may only act as an irritant to certain tissues and not to others is negatived by the contrasting appearances afforded by a primary carcinoma of the left breast and one of its metastases in the right.

If the carcinoma cell does not act as a tissue irritant, to

what then is the tissue cell proliferation characterising the primary growth due ? In endeavouring to answer this question it must first be noted that in all the specimens examined an identical type of inflammation had preceded the onset of malignancy, and that where the carcinomatous undergrowth is as yet only foreshadowed a condition of the subepithelial tissues cytologically identical with that surrounding the fully developed tumour is already present. Further, there is the fact that clinically carcinoma is initiated in the earlier and more cellular phases of the precarcinomatous states.

Thus there is both pathological and clinical evidence that the tissue cell proliferation accompanying a primary carcinoma is initiated before the onset of malignancy, a suggestion supported by the occurrence of new lymph nodes surrounded by plasma cells in the precarcinomatous state and the precarcinomatous affection of lymphatic glands. The fact that the precarcinomatous state may be led up to through a variety of forms of inflammation has already been noted, and it has been suggested that the immediate agent of this state may be the same in all cases.

Turning now to the question whether an altered state of the subepithelial tissue bears a relation to the determination of carcinomatous invasion, it appears certain that ingrowth of epithelium is closely associated with changes in the tissues underlying it, and moreover there is strong evidence that this ingrowth is subsequent to the tissue change.

For it has been shown that in the case of the cervix uteri a system of connective tissue papillæ and interpapillar epithelial processes is developed in a situation where these structures do not normally exist, and that epithelial downgrowths are initiated on local areas of plasma cell proliferation and loss of elastic tissue. And further it has been demonstrated that when the subepithelial tissue cell proliferation first takes place the epithelium is actually thinner than normal, and that its hypertrophy only develops after the subepithelial changes are established.

That which is so clearly seen in the case of the cervix is also true of the other situations that have been studied, namely, that the hypercellularity of the subepithelial tissue precedes the multiplication of the epithelial cells.

Thus the inflammatory conditions of the vulva, tongue, and skin, which in time lead up to the production of the precarcinomatous state in these situations, are at first associated with thinning or actual destruction of the epithelium, and it is only when the character of the subepithelial tissue is entirely altered that the deep interpapillar processes which characterise the epithelial hypertrophy appear.

On the Value of the Tissue Changes in relation to Primary Carcinoma.

It follows that the tissue cell proliferation accompanying a primary carcinoma cannot be regarded as protective, and this opinion is further supported by the following arguments :—

1. There is no evidence of any destruction of the active carcinoma cell by the tissue cells comparable with those seen in areas of bone necrosis or experimental tissue implantations.

2. The infiltrative character of the primary tumour is in marked contrast to the circumscription that obtains in permeated lymphatics and to a lesser extent in metastatic nodules (excepting those in lymphatic glands), in both of which latter conditions no tissue cell proliferation occurs.

3. Lymphatic glands, which alone of metastatic sites exhibit a precarcinomatous tissue cell proliferation, are earliest and most constantly affected.

4. The tissue cell proliferation results in a rarefaction of the connective tissue in front of the advancing carcinoma cells, in the course of which mechanically resistant structures such as fibrous tissue and elastic fibres become softened and destroyed.

On the other hand, whilst there is no evidence of active destruction of the carcinoma cells by the proliferating tissue cells, neither are there indications of any active destruction of the inflammatory tissue cells by the carcinoma cells. It is true that in the older parts of the growth areas in which the stroma is degenerating are often seen, but in such areas a coincident degeneration of the epithelial cells is also present.

Vigour of carcinoma cells accompanies vigour of tissue cells : senescence of carcinoma cells equally accompanies senescence of the stroma.

Conclusions.

1. The onset of the ordinary forms of carcinoma is always preceded by a condition characterised by epithelial hypertrophies and certain constant changes in the subepithelial tissue.

2. This precarcinomatous state may be attained through various inflammatory processes, at first quite distinct from one another, but culminating in the same histological picture.

3. The tissue cell proliferation occurring around a primary carcinoma is a part of the precarcinomatous process, and materially assists the progress of the growth.

4 There is no histological evidence of a protective reaction on the part of the tissues to the carcinoma cell.

5. Though changes in the adjoining connective tissue bear some very close relation to the cause of epithelial ingrowth, yet malignancy having been established the further spread of the tumour is independent of such assistance.

REFERENCES.

(1) Die Entwicklung der Carcinome. Virch. Arch., vol. cxli., p. 470 : and vol. lv., p. 67.
(2) Beitr. zur Histogenese des Carcinoms. Virch. Arch., vol. cxxxv., pp. 433–469 : and vol. cxli., pp. 153–177.
(3) Die Entstehung und das Wachsthum des Hautcarcinoms. Zeitschr. f. Krebsforschung, vol. ii., pp. 1–170.
(4) Das Krebstroma u. die Grawitz'sche Theorie der Schlummerzellen. Virch. Arch., vol. cxxxiii., pp. 147–165.
(5) Virch. Arch., vols. cxxxvii, cxxxviii.
(6) Ibid., vol. cxxix, pp. 77–108.
(7) Die Lehre von den Geschwülsten, vol. ii., 1903.
(8) Münchener Med. Woch., No. 42, 1906.
(9) Proc. Royal Soc., 1907.
(10) Rep. Imp. Cancer Research Labs.
(11) Journ. of Dermatology, Jan. 1904.
(12) Virch. Arch., vol. clvi.
(13) Zeiglers Beiträge, vol. xxvi., 1898.
(14) Arch. f. Gynäk., vol. lxiv., 1901.
(15) Trans. Royal Soc. Med., Vol. i., No. 1.
(16) Rep. Middlesex Hosp. Cancer Research Labs., No. IV.
(17) Virch. Arch., vol. clxxvi., p. 180.
(18) Verh. der Deutsch. Path. Gesell., 1899, 1900.
(19) Ibid., 1900.
(20) Virch. Arch., vol. cv., 1901.
(21) Ibid., vol. clxix.
(22) Zeiglers Beiträge, vol. xxvii., 1899.

ON SECONDARY MALIGNANT CONVERSION OF EPITHELIUM.

By ARCHIBALD LEITCH.

(With Eleven Figures in Text.)

In carcinoma growing on a surface it is a point of considerable surgical importance to recognise that the extent of the disease apparent to the naked eye by no means invariably marks the limit of local spread. Frequently there is a fairly considerable undermining of non-malignant epithelium due to a dissemination along, and upgrowth from, a deeper lymphatic network. In cases such as these there may be an over-rolling of the edges, but at any rate there is a more or less sharp delimitation of the malignant portion on the surface. The recognition of this point, practically universal, has perhaps distracted attention from the phenomena occurring at the superficial edge, and has led to the belief that a carcinoma once started from a few cells or from a small area, grows solely from that origin, and that the originally non-malignant epithelial cells bounding that focus take no part in the process of growth. But in many cases of superficial carcinoma which clinically we have seen to extend, a microscopical examination of the extending edge will fail to exhibit any sign of undermining; on the contrary, a superficial extension greater than that on a deeper plane may be revealed. That this superficial extension is not due to centrifugal expansion of the original malignant focus with an accompanying retraction of normal epithelium can be disproved clinically by observing the gradual encroachment on epidermal landmarks. In these cases it is impossible histologically to differentiate the purely malignant from the purely non-malignant portions, and we are forced to the conclusion that there has been a progressive conversion of benign to malignant epithelium. To those who have seen many extensive surface carcinomata,

as for example on the face, it will appear improbable that the condition of epithelium covering an area to which the disease may ultimately extend was *from the beginning* so far removed from the normal as to constitute that shadowy pathological entity—precancerous epithelium. In superficial carcinoma the penetration of deeper structures and the growth along lymphatics is generally the more outstanding feature; nevertheless the usually minor spread by direct continuity is not to be overlooked.

In carcinoma of the breast we can observe the growth from malignant acini along the ducts by this method of conversion. (Fig. 1.) The lumen of the duct, as we trace it onwards, may be wholly or partially occupied by proliferating epithelium, but most frequently a central channel is preserved. We can trace these ducts, unsurrounded by malignant growth, till they show a wall lined by normal epithelium. In the extension along a duct a few cells consti-

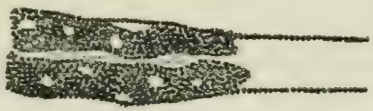


FIG. 1.—Section of a mammary duct showing the advance of carcinoma along it. This advance is held by the author to consist in a conversion of previously non-malignant epithelium into carcinoma. In the advance small areas are left untouched: one of these is seen at the side. Abortive channel formation is also seen.

tuting the original wall commonly escape this conversion, at least for a time, and these small areas form the outer boundary of a space enclosed on the other sides by a malignant epithelium less anatomically perfect. Such areas may be seen in Figs. 1 and 2. The growth from acini along the ducts may be interpreted otherwise. The channel may be considered to afford a path of extension just like a lymphatic vessel or a vein, with the difference that in the case of the duct the malignant epithelium affects a structural junction with the normal epithelium of the wall. This view would necessitate the assumption that the outermost layer of cells in such a case was normal, though their anatomical shape might be profoundly altered. There is nothing to support such a contention, but much against it.

Again, we may often see a duct passing amidst cancer masses which are closely applied to it, and only separated from them by an intact ring of elastic tissue fibres. Here there is no penetration of the wall discoverable from without, and yet there may be marked proliferation of the duct epithelium, which in extreme degree fills up the lumen com-

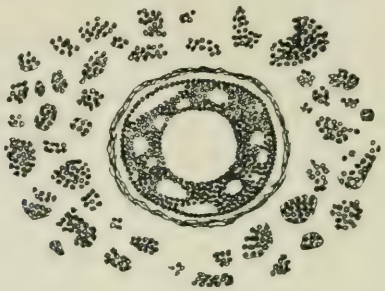


FIG. 2.—Carcinoma around a mammary duct. The elastic sheath of the duct is still intact, and the lining epithelium has proliferated, forming intramural abortive channels.

pletely, but more generally leaves a more or less diminished central channel. (Fig. 2.) This proliferation within the duct may proceed uniformly from all sides, or may show itself as an irregular projection from one part. (Fig. 3.) There are two points of importance in this proliferation to which attention may be directed: first, the appearances of the individual

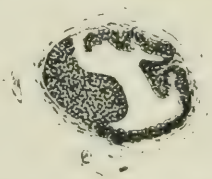


FIG. 3.—To show proliferation of epithelium commencing at one part of the wall of the duct.

cells; and second, the formation of spaces amongst them. The cubical shape of the cells lining the duct has given place to irregular formation; the cells are crowded together, irregularly polygonal, and the nuclear staining and shape are altered. In the proliferation which occurs in chronic mastitis the cells usually remain fairly large and the nucleus stains

more faintly, and it is obvious that they are undergoing some form of degeneration. In the case under discussion, however, the appearances are quite different—the cells are smaller, the nucleus is darker, and there is no degeneration. Again, amongst these proliferated cells there are generally to be found closed spaces of varying extent, unfilled by any visible material. In the cells immediately bounding these spaces the nuclei are basally arranged. The formation of these abortive lumina may be due in some cases to the retention of patches of non-malignant epithelium, as has been pointed out already, but in the more central parts they can only be explained as attempts at reproduction of their parent anatomical conformation. Such a condition as this—abortive channel formation among proliferating cells—though examined for in numerous cases of chronic mastitis and fibroadenoma of the breast, has not been found. When we find a duct through a long series of sections, preserving an unbroken elastic fibre sheath, showing a proliferation of its lining epithelium with abortive lumination, and surrounded by masses of cancer cells, the conclusion seems justified that this proliferation is malignant and is directly associated with the *proximity* to, though not continuity with, other homologous malignant epithelium. The weak point of this argument for "conversion by proximity" is the difficulty of tracing a duct with an unbroken elastic sheath surrounded by masses of cancer cells from a part where it is normal and free from surrounding malignancy to a part beyond the zone of infiltration where a similar condition obtains. Hitherto I have not succeeded in tracing a duct from indisputably normal acini to a point where it became normal again after showing proliferation as it passed through an intermediate malignant zone. The search is long and laborious, and the observations are too often rendered unreliable by the fact that normally the elastic fibre sheath ends before the acini are reached, and by the fact that there is frequently a dissolution of the fibrous tissue in cases of cancer within or around the ducts.

Coming now to the "growing edge" of carcinoma within the mamma, we may frequently observe a fairly abrupt line between the extending carcinoma and the normal portions of that organ. Commonly the disease starts in a certain lobule,

and spreading by the lymphatic channels the unrestrained epithelium invades neighbouring lobules. What happens to these lobules? Two things are at present generally admitted. The normal acini may persist for a long time, or they may disappear by pressure atrophy, and there is a replacement of the lobule by malignant epithelium of adventitious origin. But in addition to this there is a proliferation of the epithelium of the acini constituting the invaded lobule. This proliferation may be due to direct continuity with the originally malignant epithelium, either primarily existing or subsequently established, or to the proximity of the invading carcinoma. The difficulties of establishing this latter point, great as they were in the case of such well-defined structures as ducts, are increased in dealing with acini, for there is here no elastic tissue sheath to mark the boundary of an acinus, and an ultimate acinus in proliferation may not differ in microscopical appearances from a lymphatic occluded with malignant epithelial cells. Any argument, therefore, from such appearances is open to many errors. More light, however, can be thrown on the point by an examination of sections which extend from the growing edge into the more or less normal portions of the organ. As, however, growth does not proceed at the same rate in all directions, it may be a matter of chance whether we find a sharply limited margin or not. For the purposes of this research pieces of breast tissue two inches long by half an inch wide and a quarter of an inch in thickness which just included the carcinomatous edge were taken soon after removal and fixed in acetic alcohol. A few such were taken at random around the malignant nodule. On several occasions lobules near to the growing edge but separated from it by more or less intervening connective tissue stroma were found to show considerable proliferation of their epithelium; there was distension of the acini and complete filling up of the lumen. In single sections it is impossible definitely to decide whether or not some of these acini may not really be lymphatic channels distended by disseminated carcinoma cells or whether the proliferation of their epithelium was not due to direct contact with or proximity to malignant epithelium. To settle such a point it is obvious that the series must extend backwards to the origin

of the lobule and forwards to its resolution into simple ducts. The comprehensive view of such a lobule by this method entails laborious search and much disappointment, for it is by chance that one may hit upon the condition, and even then the whole lobule may not be contained within the limits of the series. The routine adopted was to cut several hundreds of sections from pieces of carcinomatous breasts and to examine every twenty-fifth section. If at any particular section the appearance was seen, the lobule could be traced backwards to its origin and forwards to its ducts. In this way I have obtained two very complete series of lobules in

FIG. 4.—Bird's-eye view of relation of lobule under investigation (A) to nearest mass of carcinoma (X). Third section after commencement of lobule.

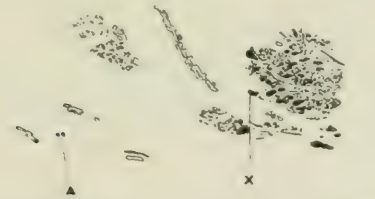
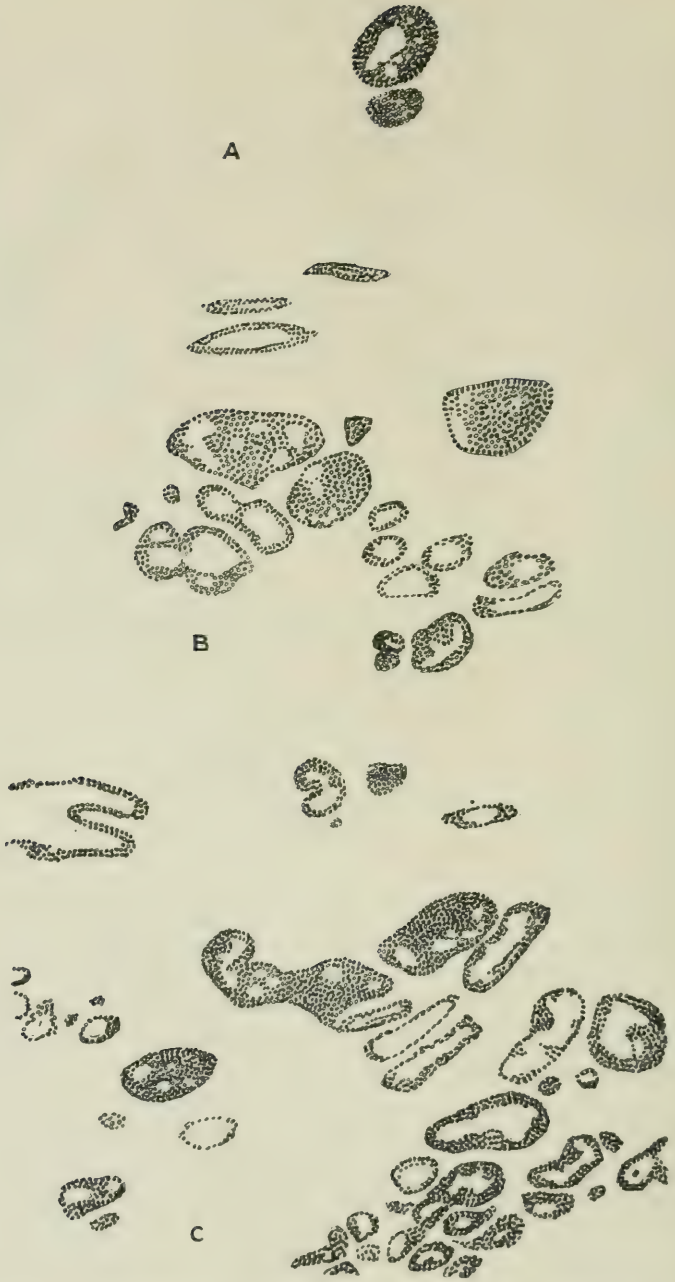


FIG. 5.—Bird's-eye view of relation of lobule under investigation (A) to nearest mass of carcinoma (X). Third section before end of lobule (No. 128).

this condition in which the intervention of any lymphatic communication with the infiltrating edge or growth by continuity along a common duct can be definitely excluded. Figs. 4 and 5 show the state of the lobule three sections respectively after the commencement and before the end, and demonstrate the distance by which the lobule is separated from the extreme infiltrating edge. These acini are distended and irregular in shape, and their lumina are encroached upon and at parts wholly filled by epithelial cells which show no degeneration. These cells here and there are formed around small closed empty spaces—an attempt at reproduction of parent characteristics. Numerous such abortive channels



FIGS. 6 to 11.—Sections of the lobule shown in Figs. 4 and 5 taken at varying distances. A, appearances at section 10; B, at section 30; C, at section 50; D, at section 70; E, at section 90; F, at section 110.

D
E
F

can be found within the bounds of a section of any one acinus. That these spaces are not the result of technique is disproved by the fixative adopted, and by the fact that the nuclei around them are basally arranged as in the cells of the normal gland. Figs. 6–11 show the development and resolution of this particular lobule. Its collecting ducts are free from all such change.

This proliferation of cells within the acini with their abortive channel formation has not been observed in chronic mastitis nor elsewhere than in proximity to a carcinomatous infiltrating edge, and is indicative of early carcinomatous change.

Conclusion.

A carcinoma having once started from a definite focus can be added to by conversion of previously non-malignant epithelium *of the same kind*—(1) in direct continuity with, (2) in immediate proximity to, and (3) within the sphere of influence of, the growing edge.

THE OCCURRENCE OF LUMINA IN MALIGNANT TUMOURS.

By L. COURTAULD and A. LEITCH.

All who are familiar with the histological appearances of malignant tumours will have been struck by the occasional occurrence of round or oval spaces, or "lumina," as they may be called, in the centre of the masses of cancer-cells. The present research was undertaken with the object of determining the origin and significance of these lumina, and of ascertaining whether they constitute a criterion for the recognition of a particular type of growth.

Material Employed.—The examination of a single section of a tumour containing lumina will give little or no information as to their origin; and this can only be obtained by means of serial sections. A series of sections, 100 to 150 in number, was, therefore, prepared from each of the following specimens: four carcinomata of the breast, three carcinomata of the cervix, one carcinoma of the upper jaw, one tumour of the palate, and one squamous epithelioma of the lip.

These sections were taken from paraffin blocks of material hardened either in acetic alcohol or in spirit. The sections were stained in a variety of ways, some by Victor Bonney's triple stain, which gave the best results,* some by Van Gieson's stain, others by hæmatoxylin and eosin or orange G.

In addition we have examined single sections of some four hundred malignant tumours received at these laboratories during the last two years.

As a result of these investigations it has been found that the lumina occurring in cancerous tumours may be separated into three groups:

i. Lumina formed by cell-necrosis.
ii. Lumina formed by irregular cell-proliferation.
iii. Lumina representing pre-existing channels.

Each of these groups will be considered in detail.

* See p. 21.

I.—Lumina formed by Cell-necrosis.

The great majority as well as the largest and most conspicuous of all lumina fall within this group. A lumen of this type appears as a round or oval space of considerable size—up to $\frac{1}{4}$ mm. in diameter—lying in the centre of the larger cell-masses This space may be empty, or may contain a certain amount of granular material, in which are embedded a number of small darkly-staining nuclei. But perhaps the most striking and characteristic feature of this variety of lumen is that it is lined by a well-defined single layer of flattened cells, which are surrounded by and continuous with

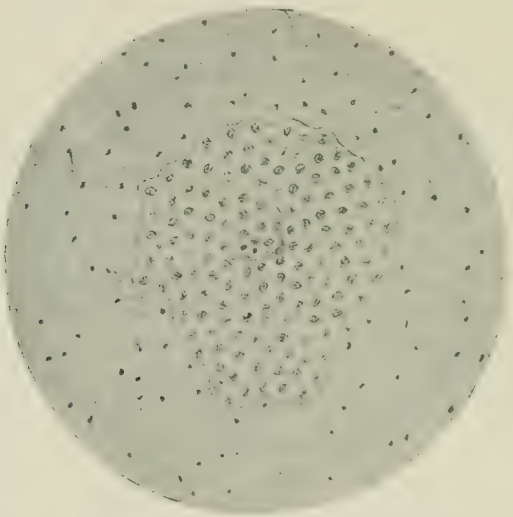


FIG. 1.—A section of a carcinoma of the breast. The cells at the centre of the malignant mass show a commencing necrosis, the first sign of lumination. (Semi-diagrammatic.)

the polygonal cancer cells composing the mass. On studying the development of these lumina by means of serial sections it was found that they are formed in the cell masses by a necrosis of the central cells. The first sign of their appearance is a loosening and dissociation of these cells, which lose their regularity of outline and their brilliancy of staining. Passing on through a series of sections this change becomes more pronounced, and affects a larger number of cells, until an irregular space, partially filled by granular débris, is formed in the centre of the mass. Eventually we arrive at a

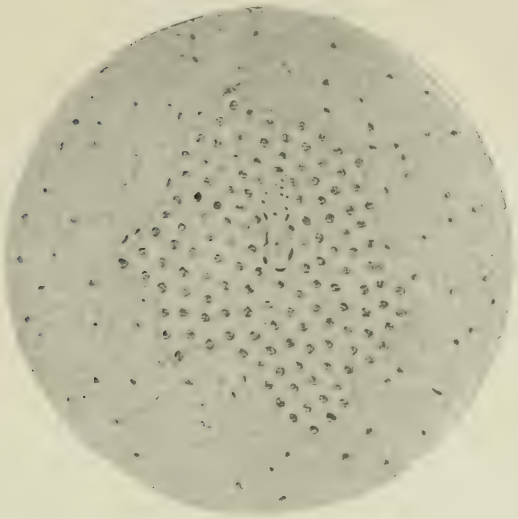


FIG. 2.—A section taken from the same block as Fig. 1 at a point about 50 μ distant. The necrotic change is more advanced, and there is some flattening of the cells surrounding the central space.

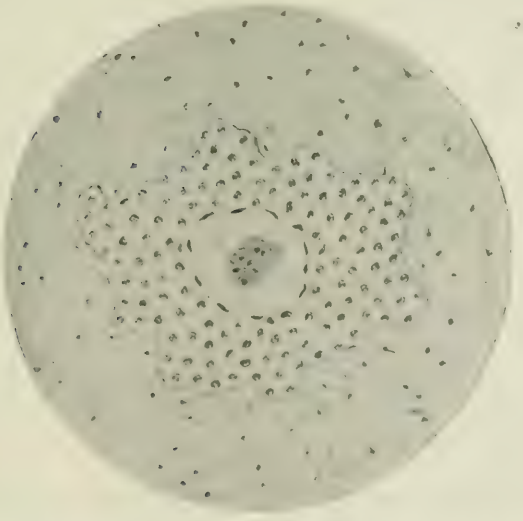


FIG. 3.—A section taken from the same block as Figs. 1 and 2 at a point about 100 μ distant from Fig. 1. Lumination is now complete.

stage where a large lumen lined by flattened cells is seen; and still further on this gradually diminishes in size, and finally ends bluntly in a condition exactly similar to that by which it commenced. A lumen of this nature can be followed through 40 or more sections, each 7 μ in thickness, and, if reconstructed in plan, would appear as a fusiform channel lying in a column of malignant cells. It seems, therefore, that the condition is produced by a fluid necrosis, that the flattening of the cells lining the lumen is due to the pressure of the contained fluid, and that the granular débris consists of degenerated cancer cells, and does not contain leucocytes as has been suggested.

Lumina of this class are seen more particularly in cancers of the breast and cervix, but they also occur in new growths of other parts. Thus well-marked lumina were found in 15 out of 63 tumours of the cervix, i.e. in 23 per cent.; in 23 out of 115 tumours of the breast, i.e. in 20 per cent.; and in 6 out of 41 squamous carcinomata, i.e. in 15 per cent.

The histological appearances of the metastases are not constant. As a rule, lumination is confined to the primary growth; at times, however, it is equally conspicuous in the secondary deposits, whilst on rare occasions it is in these latter alone that lumina are found.

A correct explanation of the particular variety of degeneration is not easy to give. It is evident that in any collection of tightly-packed cells, those at the centre will be under less favourable conditions as regards their nutrition than those at the circumference. They will, consequently, possess a lower vitality, as is shown by the comparative rarity of mitotic changes in these central cells; and will be more than usually liable to degenerative changes. It is somewhat surprising that lumination is less common in squamous-cell than in spheroidal-cell tumours; although in the former an extensive and irregular degeneration is often seen, corresponding with the fact that necrosis constitutes the physiological termination of a squamous cell.

II.—Lumina Produced by Irregular Cell-proliferation.

These are frequently seen in malignant growths of such glandular organs as the breast, and are particularly common

towards the growing edge of the tumour. They are quite small, with a diameter equal to that of two or three cells only, and cannot be followed through more than a few sections. The cells surrounding them have a radial arrangement with their nuclei at the attached margin. It is often possible to trace their formation by the union of the tips of proliferating processes of malignant cells springing from a glandular epithelium. It may reasonably be assumed that this arrangement is evidence of an attempt on the part of the cancer cells to imitate the structure of the parent tissue. It is probable that the lumina seen in columnar-cell carcinomata arise in a similar manner.

III.—Lumina Representing Pre-existing Channels.

These are of an entirely different nature from the members of the two previous groups, and have only been found in a very rare and peculiar type of breast tumour. These tumours are extremely cellular, but the great majority of the cells are entirely degenerated, and stain with plasmatic stains alone. The only cells which have escaped degeneration are confined to a narrow zone surrounding some well-marked channels, with the walls of which they are in very close connection. Some of these channels are vascular, inasmuch as they contain blood. Others are empty, and may be either vascular or lymphatic ; they do not appear to be glandular. Tumours of this nature are extremely uncommon ; only three have been found among several hundred specimens of cancer of the breast.

ON THE ACTION OF THORIUM AND URANIUM UPON CERTAIN FERMENTS.

By HECTOR A. COLWELL, M.B.

The emanations from radium have been shown by Henri and Mayer * to exert a destructive effect upon certain digestive ferments. Pancreatic juice, after an exposure of six hours, was apparently unaltered in activity, but after forty-eight hours was completely inert. Rennin, and certain other ferment-like bodies, such as oxydase and tyrosinase (Willcock †), were affected either not at all or in a very slight degree.

In view of the rapidly destructive action of radium it was considered desirable to perform some experiments, upon similar lines, with the much less active substances Thorium and Uranium. For this purpose about three grams of thorium or uranium oxide were introduced into test tubes of similar calibre, so that the surfaces of the layers at the bottoms of the tubes were approximately equal. The tubes were next filled for about three-quarters of their total capacity with the liquid under investigation, closed with an indiarubber cap, wrapped in lead foil, and allowed to remain at the room temperature. A control experiment was performed simultaneously in which similar quantities of the same fluids were placed over approximately the same volume of an inert powder (barium sulphate) in order to minimise as far as possible the question of simple absorption, a fragment of thymol being in all cases added as a preservative.

The ferment-containing liquids so examined were (1) Liquor pancreatis (B.P.); (2) Ordinary mixed human saliva; (3) Glycerinum pepsini (B.P.); and (4) Essence of Rennet (Crosse and Blackwell).

* Henri and Mayer. Comptes Rendus, 1904.

† Willcock, "Journ. Physiology," 1906.

I.—Diastatic ferments of the Saliva and Pancreatic Secretion.

For these experiments 2 c.c. of filtered mixed saliva were added to 10 c.c. of distilled water; while the liquor pancreatis was used undiluted. These liquids were exposed to thorium and uranium oxides, and control experiments made in the manner previously indicated.

The starch solution was prepared as follows: Commercial potato starch was finely powdered, then washed successively in (*a*) distilled water, (*b*) ·5 per cent. potassium hydrate solution, (*c*) 1 per cent. hydrochloric acid, and lastly again in distilled water until the liquid was perfectly neutral, the final residue being dried at 37° C. A weighed quantity was rubbed up with distilled water to form a thickish paste, which was then poured into boiling distilled water; by this means a ·5 per cent. solution of starch was prepared, which was of course opalescent. In order to determine the diastatic activity of the liquid under consideration, ·5 c.c. were added to 10 c.c. of the starch solution, and drops removed from time to time were tested with a solution of iodine in potassium iodide. During the first days of exposure neither the ptyalin of the saliva nor the amylopsin of the liquor pancreatis underwent any apparent alteration, or at least none that was not within the range of experimental error. They were accordingly allowed to remain exposed to the action of the substances mentioned for four weeks and then examined. The control fluids, which were merely placed in contact with barium sulphate, showed no appreciable alteration: those exposed to the radio-active substances showed a marked increase in the time necessary for the development of the "achromic point" or the various intermediate stages. It is, however, noteworthy that the time requisite for the preliminary stage of clarification (*i.e.*, for the formation of soluble starch) was not apparently altered. This is further exemplified by the fact that some specimens of liquor pancreatis which had been left in contact with thorium and uranium oxides for six months caused disappearance of the opalescence of the starch solution in the same time as the original control. As regards the subsequent stages associated

with the formation of dextrins and sugar, however, both samples were exceedingly feeble, the starch solutions to which they were added giving a purplish blue colour even after forty-eight hours. Two samples of saliva similarly exposed for six months had undergone decomposition and were not further examined.

These experiments were repeated on four occasions with identical results.

Table showing the relative diastatic power of samples of Saliva and Liq. Pancreatis with and without exposure to Thorium and Uranium Oxides. Temperature 16° C.

—	Time.	Control.	After Exposure to Thorium Oxide for Four Weeks.	After Exposure to Uranium Oxide for Four Weeks.
	H. M.			
SALIVA ...	– 8	Clear	Clear	Clear
	– 50	Red with Iodine	Blue with Iodine	Blue with Iodine
	1 0	Red with Iodine	Blue with Iodine	Purple with Iodine
	4 0	No colour with Iodine	Blue with Iodine	Deep red with Iodine
	24 0	Do.	Deep red with Iodine	No colour with Iodine
	96 0	Do.	Still red with Iodine	Do.
LIQ.	– 6	Clear	Clear	Clear
PANCREATIS	– 35	Red with Iodine	Blue with Iodine	Purple with Iodine
	1 5	No colour with Iodine	Blue with Iodine	Reddish purple with Iodine
	2 0	Do.	Red with Iodine	Red with Iodine
	4 0	Do.	Red with Iodine	No colour with Iodine

II.—The proteolytic ferments of the Pancreatic and Gastric Secretions.

For these experiments, undiluted liquor pancreatis and glycerinum pepsini were exposed to the action of thorium and uranium oxides, as before described. The time of exposure, however, which was requisite to produce a well-marked diminution in the power of the ferments under examination was less than in the case of the amylolytic ferments previously described. In the present experiments the exposure was for fourteen days. The digestions were carried out at the room temperature (16° C.), and 10 per cent. gelatin containing 1 per cent. methylene blue was selected as the

material for digestion. This was drawn, while warm, into narrow tubes and allowed to solidify. These tubes were then placed in test tubes containing, in the one set of experiments, 10 c.c. of ·2 per cent. hydrochloric acid with ·2 c.c. of the glycerinum pepsini under examination, and in the other set 10 c.c. of 1 per cent. sodium carbonate with ·5 c.c. of the different samples of liquor pancreatis. The length of the column of gelatin dissolved after twenty-four hours was then measured.

In the case of the glycerinum pepsini, 2·5 mm. of the gelatin were dissolved in the tube which was acted upon by the non-exposed or "control" specimen; while in the case of the thorium- and uranium-exposed specimens the lengths were ·5 mm. and ·75 mm. respectively.

Similarly in the case of the liq. pancreatis, the control showed 3 mm. dissolved, and the thorium- and uranium-exposed specimens 1 mm. and 2 mm. respectively. This experiment was repeated three times with the same result.

III.—Milk-curdling ferments of the Stomach and Pancreas.

Neither the commercial rennet nor the liquor pancreatis appeared to undergo any marked change in their milk-curdling power after one month's exposure to the oxides of thorium and uranium.

Conclusions.

1. The amylolytic ferments of saliva and pancreatic juice are reduced in activity by exposure to thorium and uranium oxides, but are still slightly active after six months' exposure.

2. The power possessed by the above-mentioned ferments of producing soluble starch is, however, not appreciably altered.

3. The proteolytic enzymes of the gastric and pancreatic secretions are likewise reduced in activity by thorium and uranium oxides, and apparently more rapidly than the amylolytic ferments. They are completely destroyed by less than two months' exposure.

4. The milk-curdling ferments are unaffected.

5. The action of thorium and uranium is therefore similar to that of radium.

THE EFFECTS OF URINARY AND BILIARY CALCULI UPON PHOTOGRAPHIC PLATES IN THE DARK.

By HECTOR A. COLWELL, M.B.

(*With Seven Illustrations.*)

The present communication is an extension of the observations upon biliary calculi which were commenced by the director of these laboratories in 1905, and published in the Fifth Cancer Report.*

Previous Work.—So far as I am aware, the only other observations of a similar character to the present are those of Russell,† who found that when certain woods were allowed to remain in contact with the sensitised film of a photographic plate, they so affected it that upon development a faithful picture of the grain was produced. Russell concluded that the results he obtained were due to hydrogen peroxide, produced by the resin of the wood. Previous to development no change was visible in the plate.

Sources of Material.—The calculi used in my experiments were, with one exception, specimens preserved in the museum of the Middlesex Hospital. The most recent were at least 25 years old, and the oldest museum specimen was one which had been removed by Percival Pott (1713–1788), and therefore 120 years old at the lowest estimate. The exception, alluded to above, was a vesical calculus found among the pelvic bones of a predynastic Egyptian body, and therefore about 5,000 years old. This specimen was kindly lent us by Mr. Shattock, who has described it in the Transactions of the Pathological Society.‡ The calculi from the hospital museum

* Lazarus-Barlow, "Fifth Report from Cancer Research Laboratories, 1906," p. 198.

† Russell, "Phil. Trans. Roy. Soc., 1904," Series B., Vol. 197, p. 281.

‡ Shattock, "Trans. Path. Soc. Lond., 1905," Vol. 56, p. 275.

had, in the majority of cases, been halved at the time they were mounted as museum "exhibits" (25 years ago); the Egyptian calculus, on the other hand, was somewhat broken, and consequently irregular in shape. The nucleus, however, was detached and had a flat face, so that it was possible to place it on a plate in precisely the same manner as our own specimens; the crust, on the other hand, owing to its irregularity, was only in contact with the plate at two or three points, and in close proximity over a small amount of surface.

Method of Experiment.—The calculi were taken to the

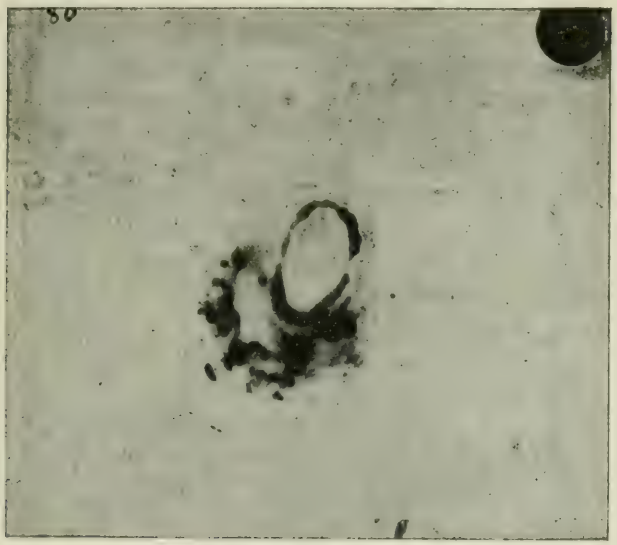


FIG. 1.—Exact reproduction of the effect produced upon a photographic plate by a uric acid calculus (No. 11 in list of vesical calculi).

dark-room and, in the case of the halved specimens, placed with the flat surface downwards upon the sensitive film of a photographic plate.* Uncut or irregular calculi were similarly placed, in the most convenient positions. The plate and calculus were next placed in successive layers of (1) thin filter paper, (2) filter paper saturated with paraffin-wax, (3) black "needle paper," and (4) tinfoil. The whole was then placed in a tinned iron box, and removed to an

* "Imperial Special Rapid" plates were used throughout these investigations.

incubator kept at 55° C. for the required time. The whole of the manipulations previous to the plate and its wrappings being placed in the box were performed in complete darkness. Development was also conducted in the dark, the "ruby" light (electric) being only turned on (1) when the calculus was removed from the plate, to determine whether any particles of the stone were adherent, and (2) briefly at intervals to watch the progress of development.

Previous to the performance of the experiments as described, a number of tentative experiments were done

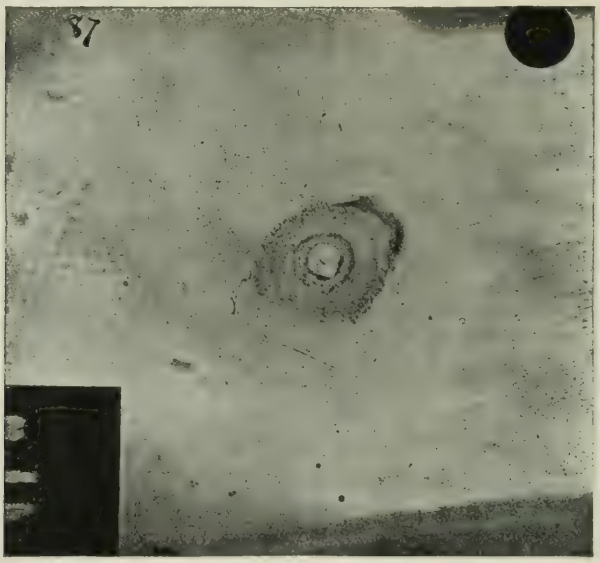


FIG. 2.—To show the effect of calculus (No. 16, vesical).

to ascertain the effects of (*a*) the length of exposure, and (*b*) previous exposure to sunlight.

(*a*) **The Effect of the length of Exposure.**—Several calculi were exposed for periods varying from 18 to 96 hours, and the depth of the shadow was found to be increased in those exposed for the longer periods. Some specimens which produced little or no effect after 18 hours' exposure, gave a well-marked shadow after 96 hours. Accordingly a uniform exposure of 96 hours was adopted.

(*b*) **The Effect of previous Exposure to Light.**—As Russell found that previous exposure to sunlight caused the woods he employed to produce a much greater effect, this question was investigated. The calculi, previously to these experiments, had been kept in the museum in glass-topped boxes, and exposed to the full effect of direct sunlight for the past five-and-twenty years. A number of them were taken and directly examined as described. They were then removed and placed in the dark for six months, and the

FIG. 3.—Reproduction of the effect produced by calculus (No. 18, vesical).

experiments repeated. No difference was seen in the two sets of experiments. Previous exposure to sunlight may therefore be regarded as without effect.

GENERAL RESULTS OF EXPERIMENTS.

Of 38 vesical calculi examined, 30 produced a definite shadow. This shadow was never larger in area than the surface of the calculus which produced it, and reproduced faithfully the appearance of portions of the calculus. The nucleus

nearly always produced no effect. In general the more porous parts of the calculi produce the best-marked effects, but this is by no means invariable.

Of the calculi which produced no effect (Nos. 3, 7, 12, 17, 23, 25, 26, 31), one (No. 3) was composed of uric acid, two (Nos. 7 and 25) of ammonium urate, one (No. 12) of uric acid with a coating of phosphates, one (No. 17) of uric acid, urates, and phosphates, one (No. 23) of uric acid, oxalate of lime, and phosphates, one (No. 26) of ammonium urate

FIG. 4.—To show the effect of calculus (No. 21, vesical).

and oxalate of lime, and one (No. 31) was an uncut oxalate of lime calculus.

Now, a reference to the table of vesical calculi (p. 107) will show that calculi composed wholly or in part of these substances may under some conditions produce well-marked shadows, but the negative results obtained with these eight specimens show that the shadows obtained with the majority of the specimens cannot be due to uric acid and urates, oxalate of lime and phosphates, *as such*.

The Biliary Calculi.—When examined as described all produced well-marked shadows. Twenty-four specimens were used for experiment, of which twenty-one were mainly composed of cholesterin and three were "pigment gallstones." The pigment stones produced a definite effect in each case, but the shadow was faint when compared with the cholesterin calculi. These latter produced in every case a well-marked effect, the shadow in each instance being larger than the area of the calculus which produced it. This local dense blackening is in striking contrast to the well-defined

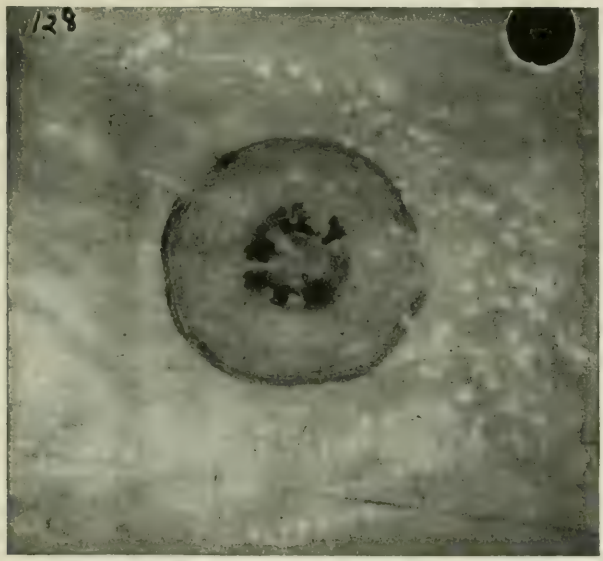


FIG. 5.—To show the effect of calculus (No. 36, vesical). The spots and the "fogging" of the outer part of the plate are accidental.

markings produced by the urinary calculi, although in some cases a certain amount of "pattern" is visible.

In order to further examine the effects of gallstones, a recent calculus was obtained from the post-mortem room, halved and examined similarly to the other specimens. It consisted mainly of cholesterin, and produced a well-marked shadow. The cholesterin contained in it was extracted and purified, dissolved in chloroform, and painted upon a plate of glass. When the chloroform had evaporated a layer of

pure cholesterin remained. This was placed in contact with the sensitive film of a photographic plate, and examined as before. After 96 hours no effect was produced upon the photographic plate. The ether-insoluble bodies in the same calculus were also examined with regard to their photographic effect, and were found to be inactive. This disappearance of the photographic effect on attempting to analyse

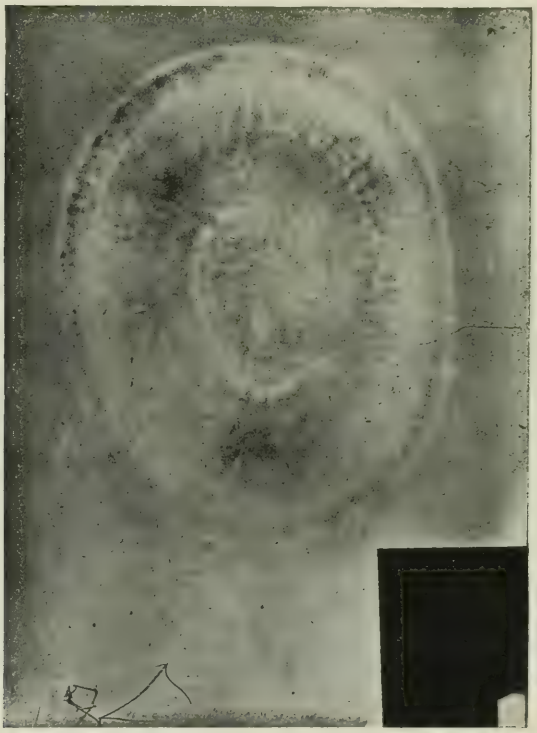


FIG. 6.—Reproduction of effect produced by calculus (No. 9, vesical, Percival Pott). It was necessary to prolong development of the plate until a certain degree of "fogging" of the surrounding portions was produced: this, however, is not so great in the original as in the reproduction.

the gallstone in question is, as yet, unexplained, but further experiments are being conducted on the subject.

The Effect of Absorption of Hydrogen Peroxide.—As it was considered possible that the effects produced might be due to the absorption of small quantities of hydrogen peroxide, the

following experiment was performed. The glass plate with the film of cholesterin, and a vesical calculus which had previously been found to be without any photographic effect (No. 26), were exposed, under a bell-jar, over a vessel containing hydrogen peroxide for twenty-four hours at 53 C. That the air above the vessel contained abundance of hydrogen peroxide was shown by its action upon potassium iodide and starch.

The plate and calculus were then removed, dried with

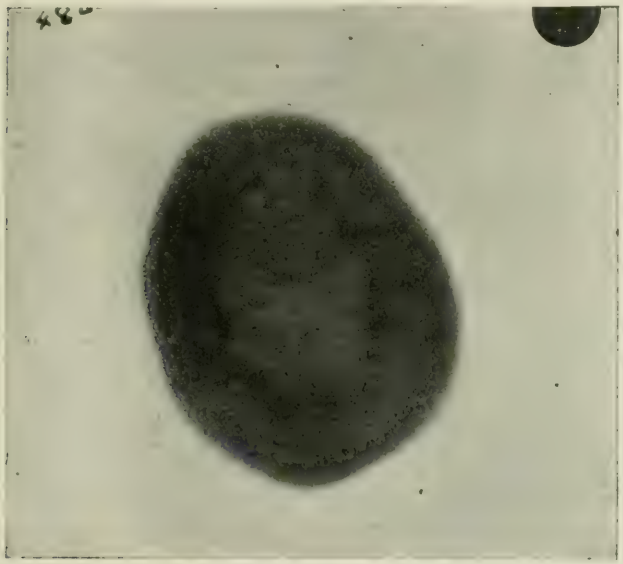


FIG. 7.—To show the effect produced by a cholesterin gallstone. The specimen had been halved and placed with its flat surface upon the sensitive film. The shadow produced occupies a much larger area than the area of the section of the calculus, the limits of which are shown by the inner dark line.

filter-paper, and examined as before. In both cases a profound effect was produced. Both plate and calculus were now exposed to the air at the ordinary temperature for about 5 hours and again examined photographically. No effect was produced in either case, so that it may be concluded that the absorbed hydrogen peroxide which produced the effect in the previous experiment had disappeared in this short time.

The Effect of Slow Oxidation of the Surface.—A biliary calculus which had been halved and kept in the museum for 25 years was examined, and produced a dark and extensive shadow. The cut face was next ground down by means of ground-glass and water, so as to expose a fresh surface, which was then re-examined as to its photographic properties, and precisely the same result was obtained as with the original face. Had the original effect been due to processes of slow oxidation, it would seem probable that the recent surface would produce considerably greater effect than the old one.

The Effect of Animal Matter.—The specimens selected for examination were, as has been stated, all over 25 years old. The selection thus made was deliberate, and intended to eliminate as far as possible the effects of any recent animal matter. However, animal matter, when dry, may be inactive as regards photographic plates,* and, moreover, in cases where an excess of animal matter might be conceived to be present (e.g., the phosphatic coats of vesical calculi), the photographic effect was absent. In addition, the gelatine film of a photographic plate of course consists of animal matter, and yet is without effect upon the silver salts.

The Effect of interposing a thin sheet of Mica between the Calculus and Film.—This was tried in many cases, including all the calculi which produced the most marked effects, but in no case was the calculus able to produce an effect through a thin film of mica.

Conclusions.

(1) Both vesical and biliary calculi may produce an effect upon a photographic plate in the dark, gallstones producing a much greater effect than vesical stones.

(2) The shadow produced by a vesical calculus in no case exceeds in extent the area of the surface which produced it.

(3) The area of the shadow produced by a gallstone is larger than the area of the stone in contact with the plate.

(4) Previous exposure to sunlight is without effect.

* Lazarus-Barlow, p. 111 et seq.

(5) In no case is the calculus able to produce an effect when separated from the film by a thin sheet of mica.

(6) The effect is not due to uric acid or urates, oxalates, or phosphates *as such*.

(7) The photographic effect cannot be considered as due to cholesterin or pigment *as such*.

(8) The photographic effect is not due to simply absorbed hydrogen peroxide.

TABLE OF THE VESICAL CALCULI EXAMINED.

Number.	No. in Museum Catalogue.	Description of Calculus.	Effect upon Photographic Plate.
1	64	Laminated calculus composed of uric acid.	The outer most compact layer of the calculus is inactive, but a more porous layer gives a definite elliptical shadow: internal to this are the marks of other more or less concentric laminæ. The nucleus gives no effect.
2	65	Oval calculus, the central portion consisting of practically pure uric acid; the surrounding portions of urates with a small amount of phosphates.	The nucleus produces no effect, a succeeding lamina produces a well-marked shadow, and the more porous periphery produces a well-marked punctate shadow.
3	67	Oval calculus of pure uric acid.	None.
4	68	Calculus of pure uric acid, laminated.	The outer portion produces no shadow, one or two of the inner laminæ a very faint shadow. The nucleus is inactive.
5	69	Pear-shaped calculus, mainly composed of uric acid, but with an oval nucleus containing much ammonium urate.	The ammonium urate nucleus produces no effect, the broader portion shows a faintly punctate shadow.
6	70	Uric acid calculus, somewhat tuberculated externally, with alternating compact (narrow) and porous (wide) zones.	The central nucleus produces no effect, the surrounding more porous portions give a punctate shadow.
7	72	Calculus showing marked lamination, and consisting mainly of ammonium urate.	None.
8	73	Laminated calculus of ammonium urate mixed with phosphates and coated externally with mixed phosphates and urates.	The nucleus is without effect, but the surrounding layer shows faint laminæ. The external layer shows a faint band.

TABLE OF THE VESICAL CALCULI EXAMINED—*cont.*

Number.	No. in Museum Catalogue.	Description of Calculus.	Effect upon Photographic Plate.
9	76	Calculus mainly composed of uric acid, porous in character, but with compact outer layer (removed by Percival Pott).	The compact external lamina of the stone gives a fairly well-marked outline. The internal more porous portions give irregular markings, and an eccentrically placed compact nucleus is without any effect.
10	78	Calculus with nucleus of uric acid, succeeded by uric acid and urate of ammonia, the external layer being more compact than the intermediate portions.	The nucleus produces no effect, but the layer immediately surrounding it gives a well-marked shadow. In the situation of the junction of the middle portion with the outermost compact layer is a distinct band. The outer layer itself is without any effect.
11	80	The nucleus and the external parts consist of uric acid, the intermediate part of oxalate of lime.	The nucleus produces no effect, but is surrounded by a well-marked dark line. Externally are numerous dark and irregular marks, corresponding to depressions in the surface of the calculus.
12	81	Calculus of uric acid with coating of mixed phosphates.	None.
13	82	Calculus of uric acid with coating of mixed phosphates.	The nucleus and outer layer give no shadows, the intermediate portions some faint concentric lines.
14	85	Calculus with uric acid nucleus succeeded by mixed phosphates and urates.	The compact central nucleus is inactive, the surrounding parts show two well-marked bands separated by a clear space.
15	86	Calculus with compact uric acid nucleus, followed by phosphate and oxalate of lime.	A shadow is produced more or less faithfully giving the outline and laminations of the calculus. The markings are, however, punctate rather than linear. The lamina surrounding the nucleus gives a darker and more linear shadow, inside which are some punctate markings.
16	87	Nucleus of uric acid coated with triple phosphates.	The nucleus shows as a clear space surrounded by a line, the succeeding clear space is surrounded by a punctate shadow.
17	88	Nucleus of uric acid and ammonium urate, succeeded by pure uric acid coated with phosphate of lime.	None.

TABLE OF THE VESICAL CALCULI EXAMINED—*cont.*

Number.	No. in Museum Catalogue.	Description of Calculus.	Effect upon Photographic Plate
18	91	Small calculus with nucleus of uric acid, succeeded by oxalate of lime and earthy phosphates.	Central nucleus clear, surrounded by dark zone. The surrounding clear space is followed by a punctate shadow.
19	92	Nucleus of uric acid, succeeded by oxalate of lime, coated with pure calcium phosphate.	Central portion clear with dark shadow nearly surrounding it, succeeded by clear space and broad punctate shadow.
20	93	Nucleus of uric acid, succeeded by oxalate of lime, coated with triple phosphates mixed with urates.	A central clear space corresponding to the nucleus is succeeded by a dark band, external to which is a fainter shadow extending to the periphery of the calculus.
21	94	Nucleus of uric acid, succeeded by calcium oxalate, coated externally with phosphates and urates.	The nucleus produced no effect, the surrounding portion shows more or less radiating shadows which appear to correspond with depressions in the surface of the calculus.
22	95	Nucleus of uric acid, succeeded by oxalate of lime, and externally by phosphates.	The central nucleus is clear and surrounded by dark concentric lines. The external portion shows an irregularly crenate shadow.
23	96	Nucleus of uric acid, followed by oxalate of lime, coated with triple phosphates.	None.
24	100	Calculus of ammonium urate	Some very faint linear markings near the periphery.
25	101	Calculus of ammonium urate	None.
26	103	Calculus of urate of ammonia covered with oxalate of lime.	None.
27	104	Laminated calculus, the nucleus of urate of ammonia, succeeded by alternating layers of oxalate of lime and urate of ammonia.	The central portion dark, surrounded by a clear zone, bounded externally by a well-marked dark line.
28	105	Nucleus of ammonium urate, coated with oxalate of lime.	The central portion is clear, and is surrounded by well-marked broad concentric bands.
29	108	Nucleus of ammonium urate, succeeded by compact uric acid, and coated with oxalate of lime.	The outer margin shows a very faint line, succeeded internally by a clear space: in the central portion is a general faint shadow not showing any differentiation of structure.

TABLE OF THE VESICAL CALCULI EXAMINED—*cont.*

Number.	No. in Museum Catalogue.	Description of Calculus.	Effect upon Photographic Plate.
30	112	Oxalate of lime calculus ...	Nucleus blank, externally some dark and irregular markings, more or less concentrically arranged.
31	113	Oxalate of lime calculus (uncut).	None.
32	114	Oxalate of lime calculus ...	Clear nucleus, the rest of the shadow showing dark radial bands.
33	115	Oxalate of lime calculus ...	Clear nucleus, the rest of the shadow showing dark radial bands.
34	118	Calculus of calcium oxalate coated with phosphate of lime.	The central portion shows varied and irregular markings, surrounded by a well-marked dark zone, outside which is a clear space surrounded by a punctate shadow.
35	121	Nucleus of oxalate of lime, followed by urates, and coated with phosphates.	The nucleus had dropped out of the specimen, and the vacant space was bounded by a layer of ammonium urate. In the situation of the absent nucleus was the only shadow produced on the plate.
36	128	Calculus of mixed phosphates and some urates.	Shows a well-marked shadow, with a radiating arrangement centrally, and a laminated structure externally.
37	129	Fusible calculus containing urates, laminated in structure.	The centre is blank. The margin well-defined, and succeeded internally by a series of well-marked concentric lines.
38	—	A calculus from the R.C.S. collection, removed from a predynastic Egyptian grave. The external portion consisted of phosphates with some urate. The nucleus which was compact and detached consisted of alkaline urates. The calculus was extremely irregular in shape, and hence only came into contact with the plate at one or two points and over a small surface.	The nucleus which was detached and had a flattened face produced no effect. The area of contact between the irregular crust and the plate shows a local deposit of silver.

ON THE EFFECT PRODUCED BY CERTAIN ANIMAL TISSUES ON A PHOTOGRAPHIC PLATE IN THE DARK.

BY W. S. LAZARUS-BARLOW.

(*With Five Figures in Text.*)

In the Fifth Report from these laboratories I published the results of experiments designed to determine whether certain substances which are generally supposed to bear a causal relation to the onset of cancer, possess characters comparable with those possessed by recognised radio-active substances. Particularising, I found that certain specimens of gallstone affect a photographic plate in the dark. Proceeding on the same lines I have investigated photographically a number of tissues derived chiefly from the human subject, and it is with these that the present paper is concerned.

Method and Material.

The method adopted was to take portions of tissue, to dry them in the hot-air chamber at a temperature of 100°–110° C. and grind them to a powder in a mortar. This powder was then extracted with ether (anhydrous and chemically pure) in a Soxhlet apparatus for six hours, dried in the air, the last traces of ether being driven off by placing the powder spread out on filter paper in the incubator for about an hour at 55° C., and preserved in a corked glass bottle. The effect of the powder was tested on Imperial Special Rapid plates. It was placed on the film directly, and after plate and powder had been wrapped in successive layers of filter paper, paraffined filter paper, and black needle paper, the package was placed in a light-tight, tinned-iron box. This was placed in the incubator at 55° C. for eighteen hours, and the plate was then developed in the usual way. In the earlier experiments all processes connected with the photographic plate were carried out in complete darkness, not even the ruby lamp

being employed, but such stringency was subsequently found to be unnecessary. The degree of blackness produced by the deposition of silver after development * was estimated by comparison with a skiagraph of a Benoist's gauge, which, since it consists of aluminium of graduated thickness, yields a shadow inversely proportional to the thickness of aluminium through which the X-rays have to pass. These shadows were arbitrarily numbered from 0 to 6, and the value to be assigned to any particular plate which had been exposed to the action of

FIG. 1.—An X-ray shadow of a Benoist's gauge used as the standard for estimating the depth of blackness in the experiments with animal tissues.

an animal tissue was determined by comparison between the experimental plate and the standard.

In the earlier experiments the powdered substance was tested on the photographic plate without undergoing a previous extraction with ether, but inasmuch as the unextracted substance was sometimes difficult to reduce to a fine state of division, and, under such circumstances, was liable to stick to

* It is important to note that no change is recognisable in the photographic film *previous* to development.

the film and injure it either that way or by the formation of a grease spot through which the developer was unable to act, it was thought better to employ ether in all cases, and the figures given in the paper itself and the protocols at the end are derived from a consideration of such ether-extracted substances.

The materials used were in the majority of cases derived from the post-mortem room, and comprised lung, liver, kidney, and spleen of non-malignant and malignant cases, the diagnosis always being made histologically. The latter were divided into classes according as metastases were absent or insignificant or were important. In all the malignant cases portions of the primary and secondary growths were taken when practicable, but since it was impossible to obtain enough powdered material for a photographic examination unless the growth was of a certain size, such a course was not always feasible. The choice of liver, lung, and kidney was made on the ground that these organs are the commonest seats of metastasis in malignant disease with the exception of the lymphatic glands. An examination of the effects of normal lymphatic glands upon a photographic plate after the method adopted was clearly impossible, and for this reason the spleen was chosen as resembling to the greatest degree the lymphatic glands. Glands the seat of metastasis were examined directly.

In addition to the substances mentioned above, examination was made in a certain number of cases of brain and other tissues.* Further, photographic examination was made of solid masses of tissue which had been dried in bulk in the hot-air chamber, and had been rubbed down to a plane surface upon sandpaper.

In all 115 non-malignant and 78 malignant cases have been investigated, while of the latter 72 were carcinomata and 6 sarcomata. The cases themselves are divided into males and females, and also into those belonging to various age-periods chosen arbitrarily for their importance with reference to the problem of malignant disease. It follows

* These will not be dealt with in the present paper. It will suffice here to state that the mean photographic value of 16 specimens of brain tissue was very high, viz. 3·9.

from a consideration of the numbers of cases that came under observation that the values obtained for carcinoma are more reliable than those for sarcoma.

The Photographic Values in Non-malignant Cases.—The actual values obtained for the photographic results in each case are given in the table at the end of the paper. From them it is seen that the greatest effect by far is produced by the liver and kidney, spleen and lung yielding evidence of photographic power in a minority of cases, and even then, with few exceptions, producing an effect of low value. These observations are equally applicable to the two sexes and at each of the age-periods.

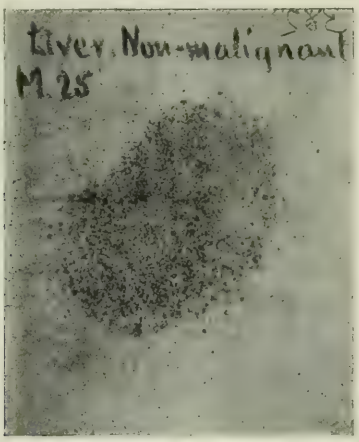


FIG. 2.—Reproduction of actual photographic plate showing the effect produced at 55° C. for 18 hours in the dark by dried, powdered, and ether-extracted liver from a man, aged 25, who died of cerebral abscess. (Photographic value of the substance = 5.)

The mean photographic values for female spleen and lung are greater than those for the male organs. But the values obtained are usually so low and the disturbing influence of a single high value in any group so disproportionate that no advantage would accrue from examining them here in age periods. Indeed, it is not certain that the occasional high values that have been obtained for these organs are entirely free from doubt. Each substance passes through a number of processes, and the total number of specimens examined is

so large (over 800) that mistakes may have arisen. Similarly, confusion of specimens may account for some of the low values obtained for the liver. As the greatest possible care has been taken to avoid such confusion I have assumed that it has not occurred, and have entered the photographic results under the appropriate columns however abnormal they might appear.

In the case of liver and kidney, however, the values are sufficiently high for approximately accurate determination. They show that the mean values in females are greater than in males. On separating the values into age-periods the following points are noticed:—The photographic value of female liver is greater than that of male liver at all age-periods until the age of 55, when the value for male liver is greater than that for female. With this exception the photographic values in the two sexes run on parallel lines both in respect of a gradual increase from infancy to age, and in respect of a fall in photographic value during the age-period 36–45.

The photographic values of kidneys are not susceptible of as simple an analysis. Though the mean value for female kidney is greater than for male when the entire series of cases is considered, this is not the case at all the age-periods. Thus in the age-periods "under 2" and 21–35 the mean male kidney values are higher than the female. Probably, however, examination of a larger number of cases would indicate that this reversal of the rule that female tissues have a higher photographic value than male is erroneous. There is no evidence that the photographic value of kidney increases with age, as appears to be the case with the liver. On the contrary, in males the values are highest before the age of 35, whereas in females, except for a high value in the age-period 36–45, they are fairly evenly distributed. Moreover the mean photographic value for the male kidney is greater than that for the liver until 20 years of age, whereas the mean photographic value for female kidney is only greater than that for liver at the age-period 36–45.

It is probable that the values obtained for the liver are more important than those of the other tissues examined from the positive side of the question by reason of the great weight

of the organ. If we consider the mean weight of the liver as being 50 oz., that of the two kidneys as 10 oz., that of the spleen as 5 oz., and that of the two lungs as 30 oz. (these figures being taken as approximate only), and multiply each value by the mean photographic value of the organ in question, an idea of the photographic value of the organ as such in the economy will be obtained. These values are as follows :—

—	Liver.	Kidney.	Spleen.	Lung.	TOTAL.
Male ...	135	20	2	15	172
Female ...	160	23	4	21	211

In other words, so far as photographic value is concerned the liver is three times as important as kidney, spleen, and lungs together.

Photographic Values of Liver, Kidney, Spleen, and Lung in Malignant Cases.—In this section it is to be noted that the tissues examined have always been free of actual growth. Of the 72 cases of carcinoma examined 41 showed important metastases (12 males, 29 females), and 31 showed insignificant metastases or none at all (13 males, 18 females). These yield the following mean values :—

—	Liver.		Kidney.		Spleen.		Lung.	
	Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.
Metastases Insignificant.	2·8	3·7	1·9	2·2	0·7	1·3	0·4	0·9
Metastases Important.	3·4	3·0	2·7	2·6	0·6	0·65	1·1	1·2
All carcinoma ...	3·1	3·0	2·3	2·4	0·65	0·9	0·7	1·1

It follows from the above figures that the superiority in photographic value held by female kidney, spleen, and lung in non-malignant cases is also held by females in cases of malignant disease, and that in both sexes liver and kidney

maintain a higher photographic value than spleen and lung in malignant as in non-malignant disease. Liver presents certain special points to which reference will be made later.

In order to institute a fair comparison between the malignant and non-malignant cases it is necessary to consider the non-malignant cases during the same range of years as that during which malignant disease is commonly met with, viz. from about 35 years onwards. This has been done in the following table:—

Mean Photographic Values of Liver, Kidney, Spleen, and Lung in Non-malignant and Carcinomatous Cases.

Age.	—	Liver.		Kidney.		Spleen.		Lung.	
		Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.
21–35	Non-malignant	3·0	3·7	2·6	2·3	1·1	1·0	0·75	0·6
	Carcinomatous	—	2·6	—	1·8	—	1·3	—	0
36–45	Non-malignant	2·7	3·4	1·6	3·9	0·3	0·9	0	0·5
	Carcinomatous	2·75	4·0	2·5	3·2	0·75	1·2	0·75	2·1
46–55	Non-malignant	3·3	4·2	1·4	2·7	0·5	0·8	0	0·8
	Carcinomatous	2·5	3·7	2·2	2·4	0	0·9	0·1	0·4
> 55	Non-malignant	3·9	2·6	2·0	2·4	0·5	1·1	0·9	0·2
	Carcinomatous	4·0	2·6	2·4	1·9	1·4	0·5	1·4	0·75
All ages above 35	Non-malignant	3·3	3·2	1·7	2·6	0·4	0·8	0·3	0·7
	Carcinomatous	3·2	3·3	2·1	2·5	0·8	0·8	0·8	1·2

From these figures the following table has been produced on the basis of the weights of the organs concerned (liver 50 oz., kidney 10 oz., spleen 5 oz., lungs 30 oz.), the values given being sums of the products of the weights into the individual photographic values:—

—	Males.		Females.	
	Non-malignant.	Carcinomatous.	Non-malignant.	Carcinomatous.
Age 21–35 ...	204	—	231	154½
Age 36–45 ...	152½	188½	228½	302
Age 46–55 ...	181½	150	265	225½
Age >55 ...	244½	273	165½	174

Hence it appears that a disproportion obtains between the photographic values in carcinomatous and non-malignant cases, but that the greater values are not always in favour of one or other condition. Thus in the age-periods 21–35, and 46–55, the total photographic value of carcinomatous liver, kidney, spleen, and lung is less than that of non-malignant organs, whereas in the age periods 36–45, and "over 55," a converse condition obtains. It is important to note, moreover, that these statements are applicable to both sexes. Reference to the values for the liver alone tend to substantiate these statements, Taking all carcinoma cases together for each sex and comparing with the non-malignant cases, the differences at the age-periods are obscured, and the values show a general tendency for a greater photographic result to be given by the organs in carcinomatous cases.

The Influence of the Mass of the Carcinoma.—Though the method of division is open to objection since the mass of a primary growth may be very considerable, separation of cases into those in which metastases are important, and those in which metastases are insignificant, affords some indication of the influence of the total mass of growth upon the photographic value of the organs under examination. This has been done in the following table :—

AGE.	Liver.		Kidney.		Spleen.		Lung.	
	Metastases Insignificant.	Metastases Important.	Metastases Insignificant.	Metastases Important.	Metastases Insignificant.	Metastases Important.	Metastases Insignificant.	Metastases Important.
Males—								
< 35 ...	—	—	—	—	—	—	—	—
36–45 ...	—	2·75	—	2·5	—	0·75	—	0·75
46–55 ...	1·8	3·5	1·4	3·2	0	0	0	0·5
> 55 ...	3·8	4·5	2·6	2·0	1·75	1·0	1	2·0
Females—								
< 35 ...	4·0	1·7	1·5	2·0	—	0	—	0
36–45 ...	4·25	3·7	2·75	3·8	1·4	1·0	1·4	3·0
46–55 ...	4·0	3·7	1·7	2·7	1·0	0·8	0	0·6
> 55 ...	2·6	2·5	2·0	1·9	0·5	0·4	0·75	0·75

The striking point about these figures (taking the liver as the most important) is that they show opposite effects in the

two sexes, importance of metastases being associated with greater photographic value of the organs in males than insignificance, but with less photographic value in females. Comparing them with the values for liver in non-malignant cases (Table on p. 117) it is seen that non-malignant liver occupies an intermediate position in both sexes. Though the matter is not fully clear it appears that the mass of a carcinoma exerts an influence upon the photographic value of the liver. Concerning the other organs investigated it is impossible to speak with certainty. As will be seen below, similar results are obtained when the liver itself is the seat of metastasis.

The Photographic Value of Carcinomatous Tissue.—In 17 cases (3 males, 14 females) it has been possible to determine the photographic value of the primary growth. For all cases taken together the mean value is 3·3, with values of 2·0 for the males, and 3·6 for the females. Of secondary growths 29 specimens from 24 cases were examined photographically (males 8, females 16), and had a mean value of 2·9, the mean values of the male and female cases being 2·5 and 3·2 respectively. Two primary and four secondary growths were entirely without effect on the plate, or the effect was doubtful; but in the remaining 40 cases, primary and secondary, an effect was produced, and, as is shown by the average, usually a marked one. Comparison of the values for males with those for females, whether the primary growth or metastases be considered, shows that the superiority of the photographic value for female tissues persists in cases of carcinoma also. In spite of the small number of cases investigated the uniformity of value for primary and secondary tumours in the two sexes (2·0 and 2·5 for males, and 3·6 and 3·2 for females) renders it probable that the above statement is true.

An attempt has been made to determine whether the presence of a growth in an organ influences the photographic value of the organ itself. For this purpose livers the seat of considerable but not universal metastases were chosen. In these, metastatic portions were carefully separated from liver which was apparently not the seat of growth, and the photographic values of the two kinds of tissue determined. This

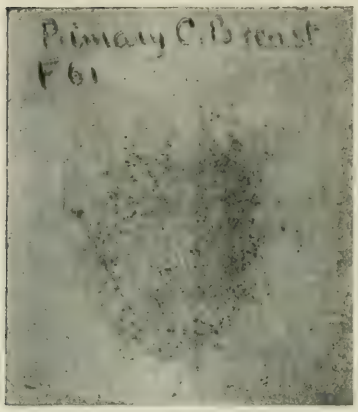


FIG. 3.—Reproduction of actual photographic plate showing the effect produced at 55° C. for 18 hours in the dark by dried, powdered, and ether-extracted primary carcinoma. (Photographic value = 5.)

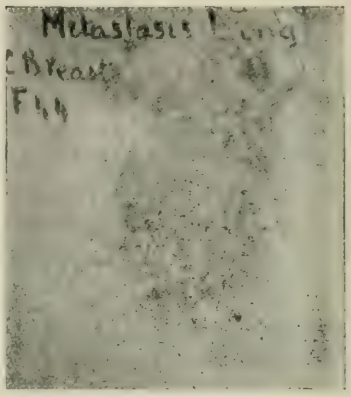


FIG. 4.—Reproduction of actual photographic plate showing the effect produced at 55° C. for 18 hours in the dark by dried, powdered, and ether-extracted pulmonary metastasis from a case of carcinoma of the breast. (Photographic value = 5.)

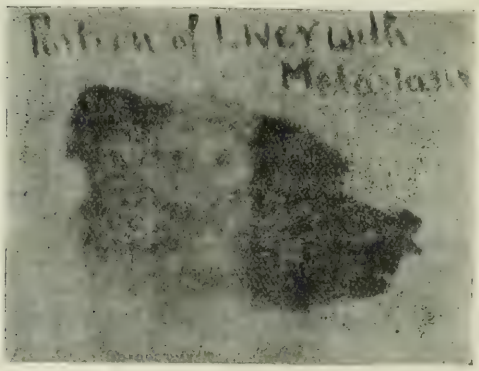


FIG. 5.—Reproduction of actual photographic plate ($\times \frac{1}{3}$) showing the effect produced by a portion of liver with a carcinomatous metastasis situated in the upper part. The slice of tissue was thoroughly dried at 100°–110° C. in the hot-air chamber, was ground to a plane surface on fine sandpaper, and was then exposed to the photographic film at 55° C. for 4 days. The metastasis shows less photographic effect than the unaffected liver, and each tissue differs in depth of effect in different places. Upon the whole the deepest effects correspond to hollows in the surface: thus in the liver itself markings indicative of branches of the portal vein are visible. Cf. Dr. Colwell's observations on Calculi, p. 98 et seq.

was possible in 15 cases (6 males, 9 females), and the mean values given below were obtained :—

—	Liver.	Liver Metastasis.	Mean Photographic Value of Non-malignant Liver for corresponding Age-Periods.
Both Sexes, all cases ...	3·2	3·3	3·3
Males, all cases ...	4·0	2·3	3·3
Males, age 36–45 ...	3·5	2·5	2·7
„ „ 46–55 ...	3·5	3·3	3·3
„ „ > 55 ...	4·5	2·7	4·0
Females, all cases ...	2·6	4·0	3·3
Females, age 21–35	2·0	5·5	3·7
„ „ 36–45	3·5	2·0	3·4
„ „ 46–55	—	—	—
„ „ > 55	2·5	3·75	2·6

Taking all cases together the only striking point is the large photographic value of the carcinomatous tissue and its practical identity with that of non-malignant liver. But on sub-dividing the cases according to sex a difference is apparent, for it is seen that the male liver bearing metastases has a greater photographic value than the non-malignant liver, while the exact converse is the case in the female. These points show themselves also when the cases are divided into age-periods. Further, the normal superiority of female liver value gives place to a superiority of male. Whether the differences mentioned above are real or are accidental, and dependent upon the small number of cases involved, it is impossible to say, but the fact that the results here given are identical in direction with those obtained when the total mass of carcinoma in the body was under consideration is an argument in favour of their accuracy.

Photographic Values in Cases of Sarcoma.—This part of the subject can be dismissed briefly on account of the few cases in which it was possible to make observations. The mean values for 6 cases were Liver 3·2, Kidney 2·8, Spleen 0·8, Lung 1·0. Primary growth (2 cases) 3, Metastases (8 specimens from 2 cases) 3·6. So far as can be said from the limited number of cases the photographic values in sarcoma do not differ from those in carcinoma.

Summary.—It follows from the evidence that has been given that certain tissues of the body when dried, pounded, and extracted with ether, produce a photographic effect under conditions of complete darkness. Amongst the organs that

have been examined liver and brain exert the greatest effect, kidney exerts some effect, while spleen and lung are without effect. These are general statements only, for examples of liver and kidney producing no effect, and examples of spleen and lung producing considerable photographic effect, are met with. The photographic value of the liver increases in both sexes from infancy to the age of 55, but after 55 increases still further in males, while it undergoes a great diminution in females. Hence in females it is at its maximum during the age-period 46–55, while in males it is at its maximum in the age-period "over 55." Further, at all age-periods excepting that of "over 55" the photographic value of the female liver is greater than that of the male. The similarity of these points to well-known facts in regard to cancer incidence is obvious.

Concerning kidney, spleen, and lung, general statements cannot be made beyond that there is a strong tendency for the values in females to be greater than those in males.

Carcinomatous and sarcomatous material, both primary and secondary, produce an effect upon a photographic plate which is about as strong as that of liver, and the superiority of female values over male for the organs is also shown in the case of female carcinomatous tissue, both primary and secondary.

The presence of carcinomatous tissue in the body appears to exert an influence upon the photographic values of the organs, whether those organs be the seat of metastases or not, and the effect produced seems to be associated in some way with the mass of the carcinoma. Nevertheless the total mass of carcinoma in the body does not modify the photographic value of the liver, for example, in the same way in the two sexes, a large mass of growth being associated with an increase of the photographic value of unaffected hepatic tissue in the male, while it is associated with a diminution of photographic value of unaffected hepatic tissue in the female. On the other hand, when the total mass of carcinoma is relatively small it is associated with a diminution of unaffected hepatic tissue in the male, and an increase in the female.

NOTE.—I have to express my gratitude to Dr. Reginald Miller, Pathologist to Great Ormond Street Hospital for Sick Children, who supplied me with much material which I could not obtain in the post-mortem room of the Middlesex Hospital.

PHOTOGRAPHIC VALUES. ETHER-EXTRACTED SUBSTANCES.

Non-Malignant Cases.

Males.							Females.						
Age.	Liver.	Kidney.	Spleen.	Lung.	Disease.	Case No.	Age.	Liver.	Kidney.	Spleen.	Lung.	Disease.	Case No.
					Age under 2 Years.								
5/52	0	3	1	0	Pyloric stenosis ...	203	2/52	0	0	0	0	Purpura	187
10/52	0	1	0	1	Marasmus	177	3/12	0	3	0	0	Postbasic meningitis (Brain 5).	199
	"spots"	"spots"											
3/12	0	4	0	0	„	184	5/12	2	0	0	0	Postbasic meningitis...	194
3/12	6	2	0	1	Postbasic meningitis	193	6/12	0	1	0	0	Marasmus	171
„	0	1	0	0	Marasmus	200	„	5	0	1	4	„	205
		"spots"											
10/12	0	3	0	0	„	180	10/12	5	2	0	3	Rickets	32
„	5	5	3	3	Laryngeal obstruction	204	11/12	5	1	4	0	Intussusception ...	209
1 6/12	4	3	2	2	Tuberculosis ...	172	1 5/12	5	2	0	0	Gen. tuberculosis ...	208
„	1	0	1	—	„ ...	195	1 5/12	3	3	0	0	Bronchopneumonia ...	196
1 10/12	1	1	—	—	Measles	123	„	6	4	4	4	„ ...	197
Means...	1·7	2·3	0·8	0·9			Means...	3·1	1·6	0·9	1·1		
					Age 2–20 Years.								
2 9/12	0	0	0	0	Accident	183	2½	0	3	0	0	Marasmus	175
3	4	4	3	0	Accident (Brain 6)...	192	3 2/12	4	6	0	1	Gen. tuberculosis ...	207
4 3/12	3	3	0	2	Empyema	188	4	6	1	0	0	Accident	151
5½	5	4	—	—	Tuberc. meningitis...	88	4¼	3	3	2	1	Pertussis	168
6	0	4	0	—	Pericarditis	114	11	2	1	0	1	Purpura	178
8	4	—	1	—	Appendicitis ...	95	16	4	3	—	—	Tuberculosis	121
9	0	0	0	0	Meningitis (Brain 3)	12							
17	0	0	0	0	Cirrhosis	140							
			"spots"										
18	0	4	0	0	Peritonitis	13							
Means...	2·1	2·4	0·6	0·4			Means...	3·2	2·8	0·4	0·6		

The word "spots" indicates that the photographic plate showed also foci of intense silver deposition.

PHOTOGRAPHIC VALUES. ETHER-EXTRACTED SUBSTANCES—*cont.*

NON-MALIGNANT CASES—*cont.*

MALES.							FEMALES.						
Age.	Liver.	Kidney.	Spleen.	Lung.	Disease.	Case No.	Age.	Liver	Kidney.	Spleen.	Lung.	Disease.	Case No.
					AGE 21–35 YEARS.								
23	5	4	1	1	M.C.	64	20	6	4	1	—	Tuberculosis	102
24	4	4	—	—	Ulcerative colitis ...	99	22	4	1	1	0	Actinomycosis ...	179
25	5	3	2	—	Cerebral abscess (Brain 5).	101	23	3	2	1	1	Appendicitis	59
							26	0	0	0	0	Uræmia	44
26	0	3	0	2	Appendicitis ...	36	27	5	4	—	—	Peritonitis	81
28	3	1	0	0	Fract. Skull (Brain 4)	26	32	6	4	—	—	Gastric ulcer	87
,,	2	4	2 "spots"	—	Pneumonia	83	,,	1	0	0	0	Pneumonia	198
							33	4	5	—	—	Appendicitis	124
,,	0	—	1	—	Cerebral disease ...	101	34	4	1	0	2	Fibroid, uterus ...	150
,,	1 "spots"	1	—	—	Dilated stomach ...	115	35	4	2	—	—	Dilated colon... ...	77
29	3	3	2	0	Peritonitis	63							
30	4	2	—	—	M.C.	96							
32	5	2	—	—	Peritonitis	76							
33	4	2	—	—	M.C.	70							
Means...	3·0	2·6	1·1	0·75			Means...	3·7	2·3	0·5	0·6		
					AGE 36–45 YEARS.								
36	5	2	—	—	Nephritis	72	36	3	4	3	2	Cholecystitis	49
38	1	4	—	—	Tuberculous laryngitis	90	,,	2	—	0	0	Peritonitis	68
41	1	1	—	—	Atheroma	108	38	5	—	0	0	Cerebral hæmorrhage	1
42	2	0	0	0	Nephritis	20	,,	3	4	—	—	Gastric ulcer	104
,,	0	0	0	0	M.C.	137	42	3	2	0	0	Alcoholism	52
43	5	1	1	—	Psoas abscess ...	92	,,	3	—	—	—	Leucocythæmia ...	116
44	4	—	0	0	Ulcers	66	43	2	6	0	0	Cirrhosis	40
45	1	0	0	0	Fractured skull ...	29	44	3	3	2	1	Pyonephrosis ...	39
	5	5	1	—	Aneurism (Brain 5)	100	45	6	4	1	1	Cerebral hæmorrhage (Brain 4).	25
,,							,,	4	4	1	0	Obesity	10
Means...	2·7	1·6	0·3	0			Means...	3·4	3·9	0·9	0·5		

					Age 46–55 Years.									
47	2 "spots"	1	0	0	M.C.	131	47	6	4	4	—	Myelitis	117
							48	5	4	0	2	Pneumonia	167
48	6	2	—	—	Bronchitis	71	„	6	2	0	0	Pneumonia (Brain 5)	191
49	1	—	—	—	Renal fibrosis ...	106	49	4	4	—	—	Pneumonia	69
50	5	3	1	0	Accident (Brain 4)...	64A	„	6	3	—	—	Cirrhosis	74
„	5	1	—	—	Peritonitis	73	50	3	3	0	1	Bronchitis	145
„	4	1	1	—	Pneumonia	91	„	1	0	0	0	„	128
52	5	3	—	—	Empyema	75	51	5	3	—	—	M.C.	86
„	5	0	1	0	Accident	136	53	6	2	—	—	Bronchitis	89
54	0	0	0	0	Cerebral hæmorrhage	133	54	0 "spots"	2	—	1	Tuberculosis	163
„	0	2	0	—	Bronchitis	135							
Means...	3·3	1·4	0·5	0			Means...	4·2	2·7	0·8	0·8		
					Age over 55 Years.									
58	5	—	0	0	Gallstones	2	56	3	3	1	1 "spots"	Subphrenic abscess ...	165
„	4	6	0	4	Cystitis	48							
60	6	3	2	4	Accident (Brain 5)...	60	58	1	0	0	0	Strang. hernia ...	149
62	3	0	3	0	HCl poisoning ...	41	60	2	2	1	0	„ „	65
„	3	1	0	0	Bronchitis (Brain 3)	173	64	4	5	1	0	Pneumonia	176
64	3	2	0	0	Cerebral disease ...	127	66	4	4	2	0	„	35
66	5	0	0	0	M.C.	8	„	5	4	1	1	Peritonitis	148
67	3	3	0	1	Strang. hernia ...	58	68	2	2	0	0	Bronchitis	174
„	2	2	0	0	Accident (Brain 3)...	61	75	0	0	0	0	„	132
77	5	1	0	0	Enlarged prostate ...	28							
82	4	—	0	—	Renal fibrosis ...	110							
Means...	3·9	2·0	0·5	0·9			Means...	2·6	2·5	1·1	0·25		
Means at all ages	2·8	2·1	0·6	0·6			Means at all ages	3·4	2·8	0·8	0·6		

The word "spots" indicates that the photographic plate showed also foci of intense silver deposition.

PHOTOGRAPHIC VALUES. ETHER-EXTRACTED SUBSTANCES—*cont.*

Carcinoma Cases. Metastases absent or insignificant.

Males.							Females.						
Age.	Liver.	Kidney.	Spleen.	Lung.	Disease.	Case No.	Age.	Liver.	Kidney.	Spleen.	Lung.	Disease.	Case No.
							Age 21–35 Years.						
		No Cases.					25	5	3 "spots"	—	—	Columnar, stomach ...	113
							34	3	0	4	0	Squamous, cervix (primary 4).	190
Means...							Means...	4·0	1·5	—	—		
							Age 36–45 Years.						
							36	5	4	2	1	Squamous, cervix ...	153
							38	4	4	2	2	„ „ ...	34
		No Cases.					39	5	2	2	0	„ „ ...	146
							42	5	4	4	—	„ „ ...	96
							43	4	1 "spots"	1	5	Spheroidal, uterus (primary 4).	154
							44	2	1	0	0	Spheroidal, breast ...	31
							45	4	3	0	1	Squamous, vulva ...	55
							„	5	3	0	1	„ cervix ...	162
Means...							Means...	4·25	2·75	1·4	1·4		

AGE 46–55 YEARS.												
47	3	0	0	0	Squamous tongue (primary 0 "spots").	134	47	4	2	2	0	Squamous, cervix ... 50
							52	4	3	—	—	„ „ 120 (primary 4).
48	3	2	0	0	Squamous, jaw ...	201						
50	1	0	0	0	„ œsophagus	51	55	—	0	0	0	Spheroidal, pancreas 55
51	0	0	0	0	Columnar, rectum ...	3						
„	0	5	0	0	Squamous, jaw ...	186						
53	4	3			„ œsophagus	84						
55	—	0	0	0	„ tonsil (Brain 4).	5						
Means...	1·8	1·4	0	0			Means...	4·0	1·7	1·0	0	
AGE OVER 55 YEARS.												
56	4	1	0	1	Squamous, tongue ...	46	56	0	3	1	3	Squamous, cervix 7 (primary 5).
61	4	2	—	—	„ bladder...	85						
63	6	5	—	—	Columnar, stomach...	93	58	3	2	—	—	Columnar, stomach 94 (Brain 3).
65	2	—	0	0	Squamous, mouth (Brain 1).	6	60	1	1	0	0	Columnar, colon ... 47
66	4	2	5	3	Squamous, jaw ...	152	65	3	0	0	0	Squamous, tongue ... 54
72	3	3	2	0	„ tongue ...	155	68	6	4	1	0	„ cervix ... 42
Means...	3·8	2·6	1·75	1·0			Means...	2·6	2·0	0·5	0·75	
Means at all ages	2·8	1·9	0·7	0·4			Means at all ages	3·7	2·2	1·3	0·9	

The word "spots" indicates that the photographic plate showed also foci of intense silver deposition.

PHOTOGRAPHIC VALUES. ETHER-EXTRACTED SUBSTANCES—*cont.*

Carcinoma Cases with Metastasis.

Males.								Females.							
Age.	Liver.	Kidney.	Spleen.	Lung.	Carcinomatous Tissue.	Disease.	Case No.	Age.	Liver.	Kidney.	Spleen.	Lung.	Carcinomatous Tissue.	Disease.	Case No.
								Age 21–35 Years.							
					No Cases.			31	1	3	0	0	... ...	Squamous, cervix	147
								34	2	2	0	0	Primary 2, hepatic 6, glands 4, kidney 1.	„ „ ...	18
								„	2	1	—	—	Hepatic 5, glands 1...	Columnar, rectum	122
Means...								Means...	1·7	2·0	0	0			
								Age 36–45 Years.							
38	0	1	0	1	... ...	Columnar, stomach	144	36	4	0	—	4	... ...	Spheroidal, breast	156
42	3 "spots"	5	0	2	Hepatic 3...	„ rectum	143	39	4	6	2	4	Glands 3	Squamous, uterus	57
								42	4	5	—	—	Primary 3, hepatic 2	Spheroidal, breast	125
43	4	3	3	0	... ...	Squamous, mouth	33	44	3	4	0	—	Hepatic 2, lung 5 ...	„ „ (Brain 3).	14
44	4	1	0	0	Hepatic 2 ...	Spheroidal, stomach	19								
								„	5	—	0	1	Primary 5	Squamous, vagina	27
								„	0	4	0	2	... ...	Spheroidal, breast	158
								45	6	4	3	4	... ...	„ pancreas	166
Means...	2·75	2·5	0·75	0·75				Means...	3·7	3·8	1·0	3·0			

Age 46–55 Years.

46	5	4	—	—	... ...	Columnar, rectum	80	46	5	3	3	2	... ...	Spheroidal, breast	38
47	5	3			Hepatic 4...	„ stomach	98	„	5	2	0	1	Primary 3	Columnar, rectum	206
„		1	0	0	„ 3...	„ „	181	47	6	4	—	—	... ...	„ cæcum	105
48	2	5	0	1	Primary 2, hepatic 3.	Squamous, tonsil...	24	48	0	0	0	0	Primary 6, lung 5 ...	Spheroidal, liver ...	202
								49	5	1	0	0	... ...	„ breast	182
„	2	3	0	—	Gland 0 ...	„ œsophagus	103	51	4	5	—	—	Glands 5	„ „	112
								53	1	4	0	0	Pleura 2, "spots" ...	„ „	167
Means...	3·5	3·2	0	0·5				Means...	3·7	2·7	0·8	0·6			

Age over 55 Years.

62	5	1	3	0	Hepatic 0...	Columnar, rectum	170	58	—	—	—	—	Primary 3	Squamous, bladder	111
66	4	4	0	5	Primary 4, hepatic 2, "spots."	„ „	161	59	6	3	0	0	Hepatic 6	Spheroidal, breast	57
								„	5	—	0	2	... ...	Columnar, rectum	157
								61	0	0	1	0	Primary 2, glands 2	Spheroidal, breast	30
71	—	1	0	1	Hepatic 6 ...	„ „	56	„	1	3	0	0	Hepatic 4	„ „	160
								„	3	3	—	—	Primary 5	„ „	82
								65	4	1	0	0	Primary 0, lung 2, breast 0.	„ „	16
								„	1	1	0	—	Lung 3	„ „	53
								„	2	3	3	0	Primary 4	„ „	62
								75	3	1	0	1	Hepatic 2, glands 4...	Columnar, rectum	22
								„	0	2	0	3	Hepatic 3	Spheroidal, breast (Brain 5).	68
								79	3	2	—	—	... ...	Columnar, sigmoid	78
Means...	4·5	2·0	1·0	2·0				Means...	2·5	1·9	0·4	0·75			
Means at all ages	3·4	2·7	0·6	1·1				Means at all ages	3·0	2·6	0·65	1·2			

The word "spots" indicates that the photographic plate showed also foci of intense silver deposition.

AN EXPERIMENTAL ENQUIRY INTO THE NATURE OF THE PROPERTY POSSESSED BY CERTAIN ANIMAL TISSUES OF AFFECTING A PHOTOGRAPHIC PLATE IN THE DARK.

(First Communication.)

By W. S. LAZARUS-BARLOW.

(*With* 18 *Figures in Text.*)

In the preceding paper I have shown that certain animal tissues possess the power of causing a change in a photographic plate under conditions of complete darkness, which is apparently identical with that produced by light. The present paper is concerned with experiments devised to throw some light on the nature of the substance or substances having that effect, and on the conditions under which it acts.

At the very commencement of the enquiry it was clear that the active substance could not be either protein as such, or blood as such, owing to the remarkable contrast in photographic activity between the liver and kidney on the one hand, and the lung and spleen on the other. Similarly the "cellularity" of the tissue could not be held accountable, since the spleen is as "cellular" an organ as the liver, though the cells are of a different kind. Further, the persistence of the activity after the tissue had been rigidly extracted with ether was proof that the active substance was not fat as such.

At this point it is necessary to point out that a fundamental preliminary to the enquiry in the case of each new reagent used was a determination of its own behaviour towards a photographic plate under similar circumstances, and it may be stated here that none of the reagents used produce such effects. This statement is particularly necessary in view of the observation made by Russell that the possession of a power to affect a photographic plate in the dark is

common to a large number of substances of a wide diversity of composition.

The following points have been made the subject of experiment:—

(1) The effect of preserving the substance in light and in darkness.
(2) The effect of exposure to air (uncovered).
(3) The effect of interposing a screen between the substance and the photographic film.
(4) The effect of various solvents.

All the above were carried out on the dried and powdered substance.

(5) The effect of precipitants.
(6) The effect of temperature.
(7) The time factor.
(8) The effect of exposure to air.
(9) The effect of exposure to light and the reverse.
(10) The effect of preserving in the moist and in the dry state.

The above were carried out on either (*a*) watery, (*b*) ethereal, or (*c*) acetone extracts of the dried and powdered substance, or of the finely minced original substance.

In addition, experiments were carried out to determine whether (11) the photographic effect is directly associated with the property of deliquescence, or of volatility as distinguished from stability of a substance; (12) it was considered in relation to the ionisation of the fluid extract; (13) in relation to the so-called "peroxydase" effect of the fluid extract or of the original substance; (14) in relation to calcium chloride; (15) in relation to tissue pigments; and (16) in relation to protein apart from peroxydase.

A—Experiments with the Dried and Powdered Substance.

(1) **Exposure to Light.**—All the specimens, some 800 in number, that have been used for the research have been preserved in the dark, in view of the observation made by Russell, that wood produces a far more intense photographic effect after it has been exposed to light, and particularly to direct

sunlight. I have found, like Dr. Colwell in his investigations upon the photographic effect produced by urinary and biliary calculi, that no difference in intensity of silver reduction is observed whether the substance, before exposure to the photographic film, has been kept in direct sunlight or in the dark.

(2) **Exposure to Air (uncovered).**—Only a small number of experiments of this type have been carried out with the dried substance, the majority having been made with extracts. To these full reference will be made later. It will suffice to state here that the effect of a free exposure to air is frequently a gradual loss of the property. A dried and powdered substance which has had a profound effect if left exposed to air will probably be found to have lost it after a period varying under a number of conditions that are unknown, but roughly in eight to ten days. On the other hand solid masses of tissue ground to a plane surface preserve the power for a long period.

(3) **The effect of interposing a screen between the substance and the photographic film.**—In view of the importance of deciding whether the photographic effect could or could not be manifested when the substance was separated from the film, many experiments were made upon the point. At the outset it may be stated that screens of the order of thickness used in similar experiments with recognised radio-active substances entirely obstruct the photographic effect of the animal tissues under consideration. Even the thinnest sheet of mica that can be detached entirely protects the photographic plate from the action of a substance that produces a profound effect when placed in contact with the film, and that though the substance has been allowed to act in an incubator at 55° C. for as long as six weeks.

This is shown by the following experiment. Seven substances were chosen which produced different degrees of effect on the photographic plate when exposed in the ordinary way in contact and for 18 hours at 55° C. To a portion of each substance two plates were exposed, the lower, with the film upwards, being separated from the substance by a thin sheet of mica, the upper with the film downwards being placed in

contact with the substance. After the pair of plates with the intervening substance and the sheet of mica had been enclosed in the various layers of paper and the tin boxes (each pair being placed in a separate box) they were incubated at 55° C. for 6 weeks, and developed. The results were as follows:—

No.	Substance.	Photographic Effect.		
		Contact 18 hours.	Mica 6 weeks.	Contact 6 weeks.
120	Non-malignant liver	6	0	6 +
57	„ „	0	0	5
42	„ kidney	4	0	6
113	Lung metastasis, carc. tonsil	1	0	5
31	Primary, carc. cervix	5	0	6 +
106	Liver metastasis, carc. rectum	2	0	5
147	Primary, carc. mamma	2	0	4
-	Control plate with mica alone	0	0	0

The result is different if the substance be separated from the film by a thin sheet of gutta-percha tissue. For under these conditions it is not uncommon to find that the plate shows a certain deposition of silver on development. It is probable, however, that the result is fallacious, for although gutta-percha tissue of itself is without effect upon the photographic plate, I have always found in those instances in which the substance has seemed to act through the tissue that the gutta-percha has undergone a loss of gloss closely corresponding in outline though not in extent to the area of the silver deposition.

In the case of solid masses of tissue which had been rubbed to a plane surface on sandpaper (cf. Fig. 5, p. 120) a thin coating of celloidin was painted over a portion of the surface. Under these circumstances the celloidin-covered portion yields a deeper photographic effect than the portion left uncovered. This result obtains both when the celloidin has been applied some six to eight hours before exposing the substance to the plate, and when it has been dried in the air for weeks. It is identical with that obtained when a portion of a cut surface of a betel nut is treated in the same way. It is possible that in the case of a recent celloidin film the photographic effect is due to an interaction of the substance and the celloidin, as has been presumed in the case of gutta-

percha, or is even due to the celloidin alone, since a recent film of pure celloidin causes a deposition of silver in a photographic plate on development. An old film of pure celloidin, however, produces no effect, so that the activity of a liver or betel nut covered by old celloidin may possibly depend upon the existence of an influence in the liver or betel which acts through the celloidin film.

B.—Experiments chiefly with Extracts of the Substances.

(4) **The Effect of Solvents.**—The following solvents for constituents of the powdered substance have been tried:—Water, ether, alcohol, chloroform, benzene, ligroin, xylol, and acetone. Of these all but water, ether, alcohol, and acetone were discarded, inasmuch as they appeared to offer no special advantages. At first, watery and ethereal extracts were used, but after it had been found that both of these extracts manifest the photographic property, they were largely replaced by the use of acetone alone. In the later experiments, too, the original substance, finely minced, was employed for obtaining the extracts and was used in the natural state and not dried at 100°–110° C. in the hot-air chamber.

The fluids obtained in these different manners differ in appearance. The watery and ethereal extracts of the dried substance vary in colour from a deep brown to a pale yellow, liver and kidney giving a deeper-coloured extract than lung or spleen, while specimens of new growth usually, but not always, afford pale-coloured extracts. Watery extracts of the natural, finely-minced tissues yield, of course, a blood-stained turbid fluid; ethereal and acetone extracts are yellow to brown in colour, and are quite clear. The properties of these extracts will be considered later.

The Solid Substance after Extraction with Water, Ether, or Acetone.—A considerable difference obtains with regard to the photographic property of the solid residue after extraction. If the substance producing a photographic effect have been previously dried and pounded, the formation of a watery or an ethereal extract alone does not entirely deprive the solid residue of its power to affect a photographic plate Thus all the values given in the preceding paper were derived from substances that had been rigidly extracted with ether.

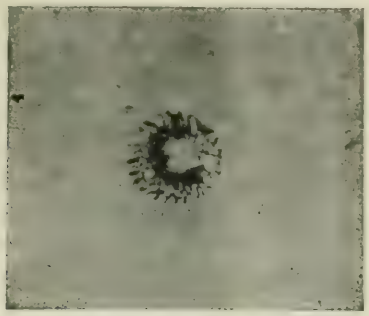


FIG. 1.—Photographic plate acted upon by a portion of betel-nut bearing a thin film of celloidin (2 years old) in the form of a crescent. The situation of the celloidin shows a greater deposition of silver on developing the plate.

NOTE.—In this and the succeeding figures the actual plate obtained in the experiment was backed with white paper and was photographed in the ordinary way with a camera. Unless this had been done the illustrations would have been in the nature of negatives.

It is further necessary to note that previous to development the photographic plate is indistinguishable in appearance from an unexposed plate.

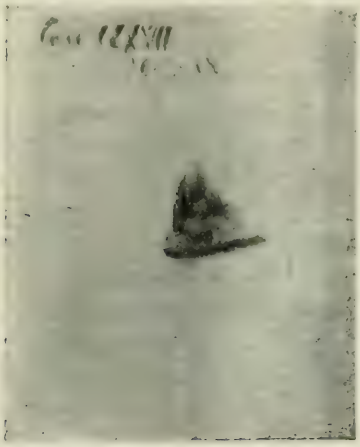


FIG. 2.—Photographic plate acted upon by a portion of liver which has been ground to a level surface and part of which has been covered with a thin film of celloidin (14 days old). The region over which the celloidin was painted shows a considerably greater deposition of silver on developing the plate, and forms the only striking part of the picture. The portion of liver not covered with celloidin yielded the faint triangular image with its base attached to the dark portion and its apex half an inch from the lower margin of the illustration.

The same holds good for a watery extraction; but if a watery extraction (with intervening desiccation of the solid residue) followed by an ethereal extraction be made, the final solid residue is found to be entirely devoid of a power to act on a photographic plate. In the case of acetone this complete removal of the photographic property takes place directly. As is seen by Figs. 3 and 4, it is found in all three instances in the extracts.

If the extraction be carried out on the natural, finely minced, but undried material, the case is somewhat different. It is true that the solid residue after extraction with acetone is without effect on the photographic plate, but in the case of water and ether extraction there is doubt owing to the fact that a satisfactory extraction with ether cannot be made in the presence of water (so large a constituent of the undried tissue) and that a satisfactory powder for placing on the photographic plate cannot be obtained after water extraction alone owing to the fat which is present. It was, indeed, largely because acetone is free from the objections to each of these solvents that it was used. It abstracts water, it dissolves fats, and it precipitates protein. Subject to these remarks it may be stated that the natural tissue both before and after extraction with water, ether, and acetone fails to yield a photographic effect. Experiments will be adduced, later, which tend to explain this apparent difference between the dried and the undried tissue (cf. p. 159 et seq.).

(5) **The Effect of Precipitants.**—In this connection watery extracts alone are under consideration.

If a watery extract of the undried, finely-minced material be made, the protein which it contains can be precipitated in a number of ways. In this research use has been made of heat, absolute alcohol, acetone, and basic lead acetate. In the case of heat, alcohol, and acetone it was simply necessary to allow the agent to act for a suitable length of time and filter off the precipitate. When basic lead acetate was used it was necessary to remove the lead in solution by passing sulphuretted hydrogen through the filtrate, and subsequently volatilise the acetic acid formed by evaporating to dryness on a water-bath.

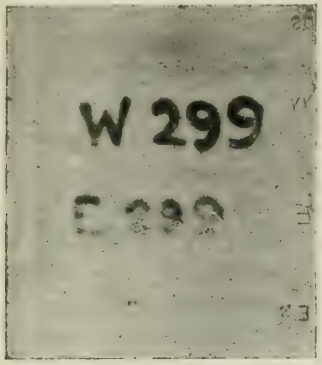


FIG. 3.—Photographic plate showing that watery and ethereal extracts of a substance contain and completely remove from a substance any photographic power it may possess. The top quarter of the plate shows an irregular deposition of silver, due to the action of the dried powdered substance 299 (liver from a non-malignant male case aged 44). The second quarter shows the action of a watery extract which was used to paint the symbols W 299 on the glass plate exposed to the photographic film. The third quarter shows the action of an ethereal extract made of the solid residue after the watery extract had been made. The irregularities in "299" are due to adhesion of portions of the extract to the film. The fourth quarter shows the absence of photographic action on the part of the substance after the watery and ethereal extracts had been made.

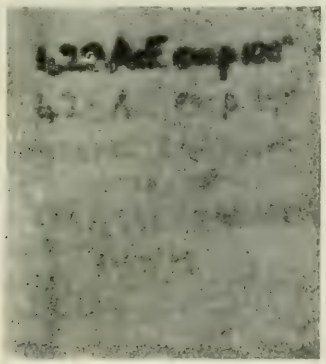


FIG. 4.—Photographic plate showing that the acetone extract of a substance may possess photographic powers. The plate shows further that an acetone extract produces greater effect if evaporated at 100° C. than if evaporated at 35° when the entire extract is considered, but that the water-soluble portion of the acetone extract does not show this difference. Moreover the water-soluble portion produces considerably less effect than the crude acetone extract. The substance 428 was squamous cell carcinoma of the cervix uteri from a woman aged 52, and the acetone extract was made of the finely divided undried new growth.

Precipitation by heat was carried out by boiling the watery solution, in some cases after rendering it faintly acid with dilute acetic acid, in others by boiling it direct. In all instances the coagulated protein was without effect upon a photographic plate; the clear yellow filtrate sometimes possessed and sometimes did not possess photographic properties. This subject is further considered below.

In the case of absolute alcohol and acetone, addition of ten to twelve times the volume of the original watery extract leads to the precipitation of a flocculent material. If washed thoroughly with the precipitating fluid the precipitate is without photographic effect. Such thorough washing is difficult, and a certain degree of photographic effect may be produced by the alcoholic precipitate in particular, even

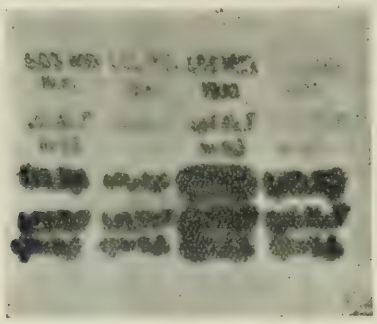


FIG. 5.—Reproduction of plate showing the photographic activity of extracts of four substances, Nos. 403 and 404 being liver and spleen of a male aged 28, and 405 and 406 being liver and spleen of a male 82.

The watery extracts of the spleens (Nos. 404 and 406) produce less effect than the watery extracts of the corresponding livers, and the liver extract of the aged man shows more effect than that of the young man. (Cf. these Archives, pp. 114–5.) The watery extracts (first and second horizontal lines) were made by allowing the finely minced original substance to stand under distilled water over-night, boiling to precipitate protein, and evaporation of the filtrate to "dryness" on a water-bath.

The alcoholic extracts of the watery extracts (third and fourth horizontal lines), made by adding a great excess of absolute alcohol to the watery extract, removal of the precipitate, and evaporation to "dryness" of the filtrate, yield photographic effects of about the same intensity as the watery extracts.

The evaporated filtrate, after treating the watery extract with basic lead acetate, filtration, and removal of the excess of lead with H_2S, yields a greatly enhanced photographic effect (fifth horizontal line), which is also shown by an alcoholic filtrate of the watery extract treated in the same manner (sixth and seventh horizontal lines).

after repeated washings. In any case, however, the degree of photographic action is far less than that possessed by the filtrate, so that there is reason to believe that it is a contamination and not a fundamental characteristic of the precipitate.

Precipitation by basic lead acetate followed by passage of sulphuretted hydrogen.—The lead salt was used in a strength of 33·3 grammes to the litre of distilled water, shaken before use, and the volume added was at least three times that of the watery extract of animal tissue. Owing to the large excess of lead present it was not necessary to filter with extreme care, as any turbidity (probably due in large measure, if not entirely, to suspended lead hydroxide in a very

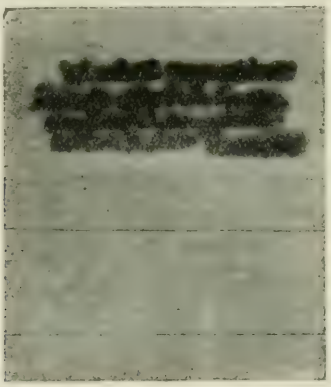


FIG. 6. Reproduction of plate showing that the photographic activity resides in the filtrates and not in the precipitates.

A watery extract of six non-malignant livers (mixed) was made. This was boiled, filtered, filtrate treated with lead acetate, filtered, H_2S was passed through filtrate, filtered, filtrate treated with absolute alcohol, yielding a filtrate and a precipitate used in the experiment of which the figure is a reproduction. The filtrate produces a deep photographic effect; the precipitate which was used to write four lines between the two horizontal black lines is without effect; on the original plate traces of silver deposition could be recognised, but were certainly due to insufficient washing of the precipitate.

fine state of division) was readily carried down in the form of a sulphide on passing the H_2S. The sulphuretted hydrogen was passed through the filtrate until the supernatant fluid was completely colourless, after which a portion of the supernatant fluid was concentrated to small bulk on a water-

bath, and was tested for lead with potassium chromate. It was found necessary to carry out this part of the experiment with care, since the presence of a small amount of lead appears to mask the photographic action, if any, shown by the filtrate. Neither the colourless precipitate of lead and protein, nor the black precipitate of lead sulphide with whatever additional materials each of these might contain, has effect upon a photographic plate.

It was thought possible that the photographic action possessed by the filtrate in experiments carried out after this fashion might depend upon the formation of an unstable protein-sulphur derivative, which subsequently split up, with the result that any action on the photographic plate under these conditions would have to be regarded as due to an adventitious substance, and not due to some direct constituent of the original watery extract. Equal portions of the original watery extract were therefore taken, the protein separated by heat coagulation, and through one portion H_2S was passed for three hours in a free stream. The fluid changed colour from a golden yellow to a dirty green. Both portions of fluid were then synchronously evaporated down to dryness on a water-bath. The dirty green colour of that portion through which the H_2S had been passed rapidly disappeared, giving place to the original golden yellow, and the dried material when tested photographically alongside the control showed no difference from the control in intensity of the silver deposition that was occasioned. The photographic effect of the fluids that had been treated with basic lead acetate, and subsequently with H_2S, was so intense, relative to that produced by the original watery extracts from which they were obtained either directly or after precipitation with alcohol, that they were largely used throughout the research in the later investigations.

The method of testing the photographic effect of fluids was in all cases the same, and consisted in evaporating them down to dryness, or nearly so, on a water bath either at 100° C. or at 35° C., or, in the case of certain acetone extracts, at temperatures varying from 10° C. to 18° C. Excepting at 100° C. the evaporation was carried out under diminished pressure. Under any of these circumstances a thick material

was produced, which was used for writing with a camel's-hair pencil on a clean glass plate. This was then allowed to dry in the air, and exposed to the film of the photographic plate for eighteen hours at 55° C. Actual contact between the characters written with the material of which the photographic effect was being determined and the photographic film was prevented by cotton threads tied round the plate bearing the writing. Thus the two plates were about half a millimetre apart from one another during exposure. In all the experiments this distance was constant. In Figs. 5 and 6 are reproduced photographic plates illustrating some of the points mentioned in the preceding paragraphs.

(6) **The Effects of Heat.**—In view of the fact that a watery extract when evaporated to dryness by simple exposure to the air of the room may not, and probably will not, produce any effect upon a photographic plate, while the same extract if it be boiled will often produce a profound effect, it became necessary, quite apart from the question of the influence of the protein in the unboiled and its relative absence in the boiled and filtered extract, to consider the effect of heat itself. It was, further, thought possible that by graduating the degree of heat to which the material was exposed certain inactive substances might be destroyed, and that the identification or isolation of the active substance might be facilitated. Experiments were therefore carried out at temperatures of 10–18° C., at 35° C., at the temperature of a water-bath (approximately 100° C.), at temperatures ranging between 100° C. and 300° C., and at a heat sufficient to incinerate the material. Bearing in mind the protein constituents of animal substances and their watery extracts, many of which begin to undergo change at temperatures far below that of a water-bath, it was possible, quite apart from the mere coagulation of protein, that changes might be produced in raising the materials above that temperature which they meet with in the animal body; in other words, it was possible that the photographic effect was brought about by an artefact.

A Temperature not exceeding 18° *C. employed.*—For investigating this point, the acetone extracts were particularly convenient, owing to the facts that the reagent dissolves the

constituents of the animal substance in which alone the photographic property resides, that it coagulates the protein, and that its low boiling point allows the process of evaporation to be carried out rapidly and easily, a very slight diminution of pressure being sufficient to produce boiling of the extract.

When an acetone extract of an animal substance, e.g. finely-minced liver, is made it is a clear, golden-yellow fluid, which, on evaporation, boils at two temperatures differing considerably from one another. The lower boiling temperature is that of the acetone itself, and as boiling progresses such constituents of the original liver as were soluble in acetone are thrown out of solution, and collect as a honey-like substance on the sides of the containing vessel or float in masses on the surface of the remaining fluid. When this boiling has come to an end the residual fluid is colourless, or at most a pale straw-colour. It consists of water abstracted from the tissue by the acetone, with those constituents of the tissue which are soluble in water or in a very dilute solution of acetone.

In practice the following course was adopted:—Having removed the honey-like solid material obtained after keeping the acetone extract at 18° C. under diminished pressure until ebullition had ceased, the remaining fluid was evaporated to dryness, still at 18° C., or the temperature was raised to 35° C. in order to hasten matters. The photographic property is manifested both by the acetone-soluble and by the water-soluble constituents of the acetone extract, the acetone-soluble portion being, however, the more potent. In this connection it must be remembered that although no temperature exceeding 18° C. was used in the preparation of the materials to be investigated photographically, the actual exposure of the film took place at 55° C. I have, however, shown previously that a photographic power shown by a substance when exposed to the film at 55° C. is also shown by that substance, though less intensely and requiring a longer time for its development in full intensity, when the substance is exposed to the photographic plate at the room temperature, and even at a temperature of − 3° C.* It appears, therefore,

* These Archives, 1906, Vol. vii., p. 199.

that the photographic property can be manifested by extracts of animal substances that have not been exposed, at any time in their preparation, to a temperature exceeding that of the human body.

A Temperature not exceeding 100° *C. employed.*—Although there is no doubt that an extract which has not been exposed to a temperature exceeding 35° C. at any period of its preparation possesses the power of affecting a photographic plate in the dark, there is equally no doubt that such a material produces a less intense effect than one which has at

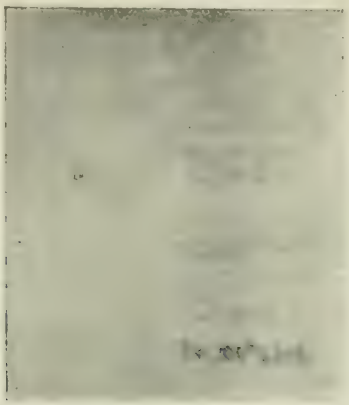


FIG. 7.—Reproduction of a photographic plate which has been exposed to various extracts as given in the accompanying key :—

424 WE evap. 35	1	...	[0]	424 WE evap. 100	1A	...	[2]
424 WE boil, filter, evap. 35°.	2	...	[2]	424 WE boil, filter, evap. 100	2A	...	[3]
1 at 35°, 4 hrs.		...	[0]	1A at 100° ½ hr.		...	[5]
2 at 35°, 4 hrs.		...	[2]	2A at 100° ½ hr.		...	[5]
424 Acetone Ext. evap. 18°		...	[3]	424 Acetone Ext. evap. 100°		...	[4]
424 AcE 4 hrs. at 35°		...	[3]	Last, 100°, ½ hr. 2A. 100°, 4 hrs.		...	[4] [6]

It is seen that the watery extract that had been exposed to a temperature of 100° C. yields a greater photographic effect than the extract exposed to a temperature of 35° : even 2A gives a greater effect than 2, while the difference between 2 at 35° for 4 hours and 2A at 100° for 4 hours is marked. The photographic values on the original plate are placed within square brackets beside each substance.

some time during its preparation been raised to 100° C., *if the extract be a watery one.* If, however, the extract be one made with acetone from the original substance, or even an acetone extract of a watery extract, the effect of a temperature of 100° C. is often the reverse, an extract which has not been raised above 35° C. during its preparation giving a more pronounced photographic effect than one which has been raised to 100° C.

A similar difference is observed between watery and acetone extracts if they are allowed to remain at a temperature of 100° C. for some hours instead of during a few minutes, as in the conditions referred to in the preceding paragraph. In the accompanying reproductions it is seen that the

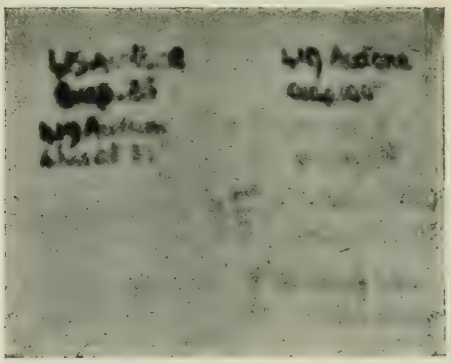


FIG. 8.—Reproduction of a photographic plate which has been exposed to an acetone extract under the conditions given in the accompanying key :—

419 Acetone evap. 35°	[6]			419 Acetone evap. 100	[5]
419 Acetone 4 hrs. at 35°	[5]	4 hrs. 100°	[2]	419 Acetone ½ hr. at 100°	[3]
419 WE, evap. 35 AcE, evap. 35°	[2]	2 hrs. 100°	[4]	419 WE evap. 35° AcE, evap. 100°	[2]
419 Ether Ext. evap. 35°	[2]	1 hour 100°	[3]	419 Ether Ext. evap. "100°"	[3]

NOTE.—The symbols "4 hrs. 100°," "2 hrs. 100°," "1 hour 100°" were written with the extract against which they are placed, after that extract had been exposed for 4, 2, and 1 hour respectively to the temperature of 100° on a water-bath. In the 5th and 6th horizontal lines an acetone extract of the watery extract was used. The photographic value of each substance on the original plate is given within square brackets.

watery extract undergoes a progressive increase in photographic activity with an exposure to a temperature of 100° C. On the other hand, prolonged exposure to a temperature of 35° C. does not modify the intensity of the photographic effect. In the case of acetone extracts exposure to a temperature of 100° C. for some hours leads to a marked diminution of photographic effect, while slight diminution is caused by exposure of the acetone extract to a temperature of 35° C. for some hours. The above points are illustrated by Figs. 7, 8, and 9.

In the case of most extracts, a fluid which is colourless or nearly so prior to complete dehydration on the water-bath

FIG. 9.—Reproduction of a plate which has been exposed to substances as indicated in the accompanying key. The photographic value of each substance on the original plate is placed within square brackets :—

426 AcE evap. 100° ... ... [3]
426 AcE evap. 35° ... ... [4]
426 AcE 35°, Acetone-Sol. part evap. 35 ... ... [2]
426 AcE 35°, H_2O-Sol. part evap. 100° ... ... [3]
426 AcE 35°, H_2O-Sol. part evap. 35° ... ... [2]
426 WE AcE evap. 100° ... ... [1]
426 WE AcE evap. 35° ... ... [3]
426 WE AcE 35°, H_2O-Sol. part evap. 100 ... ... [2]
426 WE AcE 35° H_2O-Sol. part evap. 35 ... ... [1]
426 AcE, $CaCl_2$, Acetone-Sol. part evap. 100 ... ... [6]
426 AcE, $CaCl_2$, Acetone-Sol. part evap. 35° ... ... [6]

becomes deep brown with the disappearance of the last traces of water. Fig. 10 shows that this change of colour is not accompanied by any noteworthy alteration in the photographic value.

Exposure to temperatures varying from 100° *C. to* 300° *C.*—Exposure of the substances producing photographic

effects in the dark to temperatures from 100° to 300° C. was carried out upon the semi-solid residue obtained by evaporating (*a*) watery extracts, (*b*) acetone extracts, (*c*) acetone extracts of watery extracts, (*d*) and (*e*) acetone and acetone of watery extracts respectively that had been shaken up for several hours with a large excess of $CaCl_2$, and were therefore anhydrous.

The exposure to heat was carried out in two ways. In a first set of experiments, a certain amount of the material was placed in a thin-walled test-tube of small diameter, which was immersed in a beaker of sulphuric acid. The tube was removed when the temperature of the acid had been raised to

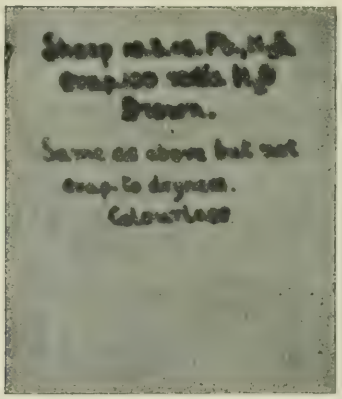


FIG. 10.—Reproduction of plate showing that the change in colour which occurs in the last stages of evaporation at 100° is not accompanied by any noteworthy alteration in the photographic value, and particularly that it is not the cause of the photographic effect.

various heights, and portions of the material were taken for photographic investigation. The advantage of this method is that the material which has been heated can be subjected to the action of various reagents, as will be indicated below. The disadvantage is that it is impossible to be certain that the whole of the material has reached the temperature of the acid. Moreover, after heating material to, say, 150° C. and taking out a portion, the sulphuric-acid bath and the material itself have fallen in temperature, so that re-immersion of the tube in the acid and re-heating to, say, 160° C., does not give a fair indication of the effect on the material of a rise of 10° C. In later experiments, therefore, the following plan was

adopted. A small hot-air chamber was made, which carried suspended in the centre a wire-gauze platform. At a little distance from the centre of the platform the gauze was pierced to allow the passage of a thermometer. The substance to be heated was painted with a camel's-hair pencil on a No. 1 coverslip, and was then placed on the platform, and heat to the required amount, as determined by the thermometer, applied. Owing to the thinness of the glass coverslip and of the layer of material painted thereon, it is probable that the temperature to which the substance attained was very close to that indicated by the thermometer at the same moment. In practice the temperature was run up as rapidly as possible, and kept at the required point for five minutes. When all the coverslips constituting an experiment had been heated, they were fastened to a sheet of glass with a small drop of seccotine (which is without effect on a photographic plate) placed on the posterior surface. The entire sheet of glass was then exposed to a photographic plate in the ordinary way.

In the following table are given the results obtained in two consecutive experiments carried out after the last-mentioned method, while below is reproduced one of the actual photographs obtained. (Fig. 11.)

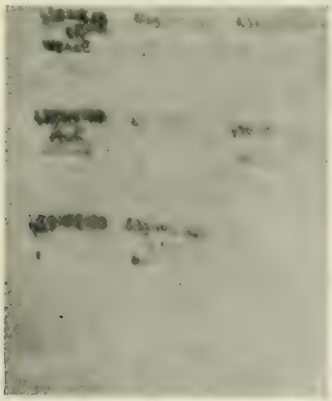


FIG. 11. Reproduction of plate showing the effect of temperature on various extracts of Substance 439. Compare with first half of succeeding table. The increasing temperatures are to be read in vertical columns from above downwards and from left to right.

Table showing the Effect of Heat varying in Intensity from 18° C. to 300° C. on various Extracts of Animal Substances.

Temperature	18° C.	100° C.	150° C.	200° C.	220° C.	240° C.	260° C.	280° C.	300° C.
—	Photographic Value.	Photographic Value.	Photographic Value.	Photographic Value.	Photographic Value.	Photographic Value.	Photographic Value.	Photographic Value.	Photographic Value.
439, Liver.									
WE	5	5	5	4	4	4	4	4	3
AcE	5	4	1	1	?	1	1	?	2
WE, AcE	5	4	2	2	1	2	2	3	2
AcE, $CaCl_2$	3	2	1	1	?	0	0	0	0
WE, AcE, $CaCl_2$	0	0	0	0	0	0	0	0	0
440, Growth in Liver.									
WE	4	4	1	3	2	2	2	2	2
AcE	3	2	?	?	1	2	2	2	2
WE, AcE	3	2	1	1	1	2	2	2	2
AcE, $CaCl_2$	6	6	6	0	0	?	0	0	0
WE, AcE, $CaCl_2$	0	0	0	0	0	0	0	0	0

NOTE.—"WE" stands for "watery extract," "AcE" for "acetone extract," "WE, AcE" for "acetone extract of a watery extract." The addition of "$CaCl_2$" indicates that the corresponding extract has been rendered anhydrous by prolonged shaking with a large excess of the salt. The value assigned to the photographic result was determined by reference to the standard as described on p. 112.

From the foregoing table it appears that the photographic property is highly resistant to heat and that it is not equally resistant in the different extracts. Thus the watery extracts and the acetone extracts of the watery extracts in both cases show a greater resistance than the acetone extract. Further, the relative constancy over a large range of temperature is remarkable, bearing in mind that the material becomes thoroughly charred at a temperature of about 200° C. The acetone extract treated with calcium chloride shows a complete destruction of the photographic property at a temperature between 150° and 200°. Reference is made to these extracts later.

If a mass of the inspissated watery extract of a substance which yields a good photographic result be heated in a sulphuric acid bath to a temperature of 200° C. it undergoes a complete charring. If now it be removed from the bath and water be added the mass only partially dissolves and a muddy fluid results. On filtering this a deep brown clear filtrate is obtained which yields a precipitate with absolute alcohol. The insoluble portion of the muddy fluid is with-

out effect upon a photographic plate: the filtrate exerts considerable effect. With regard to the filtrate and precipitate after addition of alcohol to the filtrate from the muddy fluid, there is no doubt that the filtrate possesses photographic power, but the case is not so certain with regard to the precipitate. The alcoholic precipitate is generally crystalline, the crystals being very inconstant in shape and undergoing deliquescence when being watched under the microscope. In this precipitate prisms, cubes, regular octahedra, sheaves of needles like those of tyrosin, rosettes and hexagons have all been met with, but they are all characterised by a great avidity for water, by being largely composed of carbon, as determined by their charring with heat, and by their failure to produce a photographic effect. Throughout the entire research it has been found that the photographic effect is wanting from the crystalline portions and is present in the non-crystalline portions of extracts. An attempt was made to obtain salts of the unstable crystalline substances in the hope that they would be more stable, but without success.

The final filtrate after addition of alcohol to a watery extract heated to about 245° C. yields, on concentration over a water-bath, a honey-like, highly deliquescent material which on repeated re-solution in water frequently deposits material chiefly crystalline at first, but, owing to deliquescence, rapidly becoming amorphous, which is without effect upon a photographic plate. At the present time no further analysis of the honey-like material can be given, but it is under investigation.

Exposure to a heat sufficient to incinerate the material. This was carried out by applying the blow-pipe flame to a small quantity of either the original substance or of a watery extract in a platinum dish. Although there is no doubt that a deep photographic effect may be produced by an animal tissue or a watery extract thereof which has been charred, there is equally no doubt that complete combustion with destruction of the carbon present entirely destroys the photographic property. It has already been shown that that property persists up to a temperature of 300° C., but no statement can be made as to the temperature between 300° C. and the temperature of the blowpipe

at which the disappearance takes place. It would appear from this that the photographic property is not bound up with the inorganic constituents of the tissues, but with the organic.

Exposure of the substance to the photographic film at a temperature of 100° *C. in dry air.*—In the following set of experiments the substance was placed in contact with the photographic plate, and was kept throughout the exposure at a temperature of 100° C. in the hot-air chamber. The results were not entirely satisfactory, as the photographic plate itself undergoes change, and when developed shows a general "fogging." When the plate is exposed to the substance for 18 hours this fogging is so intense that the effect of the substance itself can only be discerned with difficulty. However, on placing the plate before a very strong light it can be seen that the part on which the substance has lain is blacker than the rest. By diminishing the length of exposure the effect can more clearly be brought out, and if the substance be exposed to the plate at this temperature for half an hour only, the part over which the substance lay shows a definitely greater silver deposit than the parts around. It is therefore clear that a temperature of 100° C. in a dry atmosphere does not prevent the photographic action.

(7, 8 and 9) **The Time Factor—Effect of Exposure to Air and to Light.**—One of the great difficulties that has beset the research is the fact that the photographic property of the extracts of animal tissues, if inspissated to the greatest possible extent ("dryness"), is not a constant one, but on the contrary undergoes a diminution that is very variable in its rate, and ultimately leaves an extract that formerly possessed powerful photographic properties completely devoid of them. This diminution of effect characterises all varieties of extract alike, but appears to be most rapid in the case of watery and acetone extracts, less rapid in the case of ethereal extracts and in watery extracts that have been treated with basic lead acetate and subsequently with H_2S.

A curious point with reference to the diminution in photographic effect is that it is by no means uniform. Although the final state to which an extract comes appears to be one in which it produces no photographic effect, such a condition is preceded in a considerable number of cases by a condition of oscillation, the effect being now greater and now less. Hence it appears that an actual augmentation of power may take place from time to time. This point is shown by the experiment given below in which the same plate was exposed to a photographic film at various periods after the initial exposure.

		Photographic Value			
		On Dec. 19.	On Jan. 9.	On Jan. 21.	On Feb. 4.
Watery extract of 439	1	6	6	6	0
	2	6	6	6—5	0
,, ,, 440	1	5	5—3	1	0
	2	5	4—2	0	0
,, ,, 442	1	3	3—2	0	0
	2	3	2	0	0

		Photographic Value			
		On Dec. 19.	On Jan. 9.	On Jan. 21.	On Feb. 4.
Acetone extract of 439	1	2	5	1	0
	2	3	6	2	0
,, ,, 440	1	3	5	1	0
	2	2	3	0	0
,, ,, 442	1	2	4	0	0
	2	2	4	0	0

		Photographic Value			
		On Dec. 19.	On Jan. 9.	On Jan. 21.	On Feb. 4.
Alcohol extract of 439	1	4	6	0	0
	2	4	6	1	0
,, ,, 440	1	3	3	1	0
	2	2	1	0	0
,, ,, 442	1	2	3	0	0
	2	2	1	1	0

Thus at a time when the watery extracts were remaining constant or diminishing in photographic activity (Dec. 19–Jan. 9) the acetone and alcoholic extracts were increasing in activity. And, further, whereas the watery extract of 439 remained stationary in activity between Jan. 9 and Jan. 21, the acetone and alcoholic extracts underwent a marked diminution.

The following set of figures and illustrations obtained by repeated re-exposure of the same plate shows the same points in the case of ethereal extracts of four samples of carcinomatous tissue. It is noteworthy that the photographic power of the *watery* extracts of the same four samples was lost within a fortnight of their preparation.

No. of Substance.	Nov. 15.	Nov. 21.	Dec. 14.	Jan. 15.
31 E	6	0	2	0
67 E	6	0	2	0
75 E	4	2	3	0
106 E	0	0	?	0

The result mentioned above was so unexpected that further experiments were made upon the point. It was thought possible that the loss of power was due to a progressive volatilisation or oxidation of the active substance, and that the return of activity was due to the accidental presence of traces of the original animal substance which gave the property to the extract, and which with time had led to an accumulation sufficient to produce an effect on re-exposure of the plate, but dissipated by a temperature of 55° C. continued for eighteen hours. The following experiment was therefore made: Substances 439, 440, and 442, the acetone extracts of which possessed respectively photographic values of 5, 4, and 3, were left under acetone for twenty-one days in order to extract as much of the active substance as possible. It had already been ascertained that the solid residue after exposure to the action of a large

quantity of acetone overnight yielded no photographic result when tested immediately, but the point was specifically determined for the residues in question. At the end of twenty-one days the solid residue was filtered off, repeatedly washed with acetone, and then allowed to stand under acetone for a further period of four days. This second extraction and the first acetone extract that had been in contact with the substance for twenty-one days were then examined photographically on a number of successive days. The results are as below.

—	Jan. 13.	Jan. 14.	Jan. 15.
Second acetone extract of 439 (4 days old) ...	1—2	0	0
,, ,, 440 ,, ...	1—2	0	0
,, ,, 442 ,, ...	1—2	0	0

—	Jan. 9.	Jan. 11.	Jan. 14.	Jan. 16.	Jan. 21.	Feb. 4.
First acetone extract of 439 (21 days old).	0	4—2	0	0	0	0
First acetone extract of 440 (21 days old).	0	2	0	0	0	0
First acetone extract of 442 (21 days old).	0	2	0	0	0	0

It appears therefore that the first acetone extracts had completely lost their power of affecting a photographic plate as the result of twenty-one days' standing on the original substance, that recrudescence of photographic power is a property of the acetone extract itself as distinguished from the original substance, and that a certain degree of photographic power is conferred on acetone by its action for four days on a material which appeared to have entirely lost a photographic power it originally possessed.

A similar experiment was carried out with the acetone extracts of the watery extracts of substances 439, 440, and 442. In this case the watery extract had been removed

from the original finely minced substance the morning after its preparation, and the acetone had been added immediately. The photographic values of these acetone extracts of watery extracts on the first day of their formation were respectively 5, 4, and 4. The acetone was allowed to stand on the precipitate which it threw down from the watery extract for twenty-five days, after which a plate was prepared and was examined photographically on successive days. The results were as follows:—

—	Jan. 13.	Jan. 14.	Jan. 15.	Jan. 16.	Jan. 17.	Jan. 21.	Feb. 4.
Acetone extract of watery extract of 439 (25 days old).	5	2—3	5	5	5—3	0	0
Acetone extract of watery extract of 440 (25 days old).	3	1	<1	<1	trace	0	0
Acetone extract of watery extract of 442 (25 days old).	3—4	1	<1	<1	trace	0	0

A marked difference therefore shows itself between the acetone extract and the acetone extract of the watery extract, the former losing practically its photographic power as the result of standing on the original substance from which it was made, the latter preserving that power relatively unimpaired.

A further point that was considered carefully in connection with the recrudescence of photographic power was the possibility that it might depend upon exposure to light or preservation in darkness, but experiment showed that neither condition affected the result. Thus in the experiments detailed above the plates under investigation were preserved in the dark until January 21st, and from the 22nd till February 4th directly in front of the window.

(10) **Preservation in the relatively dry and in the moist state.**—Owing to the honey-like consistency of the extracts obtained from the animal substances it is impossible to speak of them as being preserved in a "dry" condition in the same way as it is possible with the powdered substances themselves after they have been exposed to the action of air at 100°–

110° C. The term "inspissated" is therefore preferable, meaning thereby that the extract has been evaporated on a water-bath as far as possible. Reference has already been made to the fact that these extracts lose their activity within a relatively limited number of days. In the case of extracts that have been evaporated down to a point considerably short of this, and have been kept in small bulk in a stoppered bottle, the loss of activity is far less. Thus the acetone extracts of the watery extracts of substances 439, 440, and 442 yielded a photographic result of value 2 on the 82nd day after their original preparation, and a watery extract of sheep's liver that had been treated with basic lead acetate and subsequently with H_2S has preserved its photographic value of 6 unchanged for 97 days. Preservation of the extracts in these two ways is the most convenient; it is only necessary to take a small quantity as occasion arises and evaporate it to "dryness." Preservation of the watery extracts themselves is almost impossible by reason of putrefaction, and it has already been shown that the acetone extracts that have been allowed to stand on the finely minced original substance have lost their photographic activity within a relatively short time.

(11 and 12) **Relation of the photographic activity of a fluid to its ionisation—Deliquescence, Volatility.**—It was thought possible that the photographic activity might be due to the presence in the fluid of a number of free ions that were able to affect the plate, and that the loss of photographic power might be due to the disappearance of these free ions either by entering into some relatively stable combination, or by their passage into the air and dispersal.

That the mere physical properties of volatility and deliquescence are not accountable for the photographic effect was shown by the following experiments. The question of deliquescence was examined by exposing a number of deliquescent substances, of which calcium chloride and glycerine were the most striking, to a photographic plate. These substances were completely without effect. It appeared therefore that the photographic effect manifested by the extracts of the substances did not depend upon their non-crystalline and

deliquescent nature as such. The question of volatility was considered in another way. There is no doubt that all the animal substances, whether in the form of dried powders or in that of a fluid extract, possess a peculiarly penetrating odour which differs with the different tissues to some degree and is particularly evident in the case of liver. If the photographic effect were due to this volatile substance or substances it should be possible to obtain their action on a photographic plate, apart from the action of the solid portions of the substance, by allowing a current of air which had passed through a chamber containing a quantity of the substance to impinge upon a photographic plate placed at a distance. A bottle to contain some of the substance to be examined was therefore fitted with two glass tubes for inlet and outlet of air. The inlet tube was connected with a cylinder of compressed air and the outlet with a metal tube soldered into the lid of one of the tinned-iron boxes used to hold the photographic plates when they were being exposed to the action of a substance in the incubator at 55° C. This metal tube ended in a point that was pierced with a fine hole and was bent at a right angle on the inner side of the lid of the box so that a stream of air emerging from the pinhole would impinge directly on the photographic film. The whole apparatus having been set up a current of air was passed on a photographic plate for eighteen hours in the incubator, the passage of the air being determined both by the sound it made when escaping and by placing the exit point of the metal tube under water before the commencement and after the termination of exposure of the photographic plate. Air which had passed through the entire system was completely without effect on the plate even though the air was saturated with moisture. Quantities of essential oil of cloves, of oil of thyme, of oil of cajeput, and of oil of cedar wood, were then successively examined, and it was found that whereas the air charged with the volatile substances from the oil of cedar wood produced a profound effect upon the photographic plate. air charged with the volatile portions of the other essential oils was without effect. Examination in the same way of substances 420 and 424 (each of which yielded a photographic

result of value 5 when placed on the plate in the ordinary way) showed that the volatile substances from these animal tissues were completely without action on a photographic plate.

The experiments upon the relation of the photographic activity to the ionisation of the fluid were carried out in the following way. Having chosen methyl orange as the indicator for the reason that the acetone used was basic thereto, 2 cc. of the methyl orange solution was added to a mixture of 200 cc. water and 5 cc. acetone. This was then divided into two equal parts, of which one was strongly acidified, and the other was carefully titrated with N/50 H_2SO_4 until the tints of the

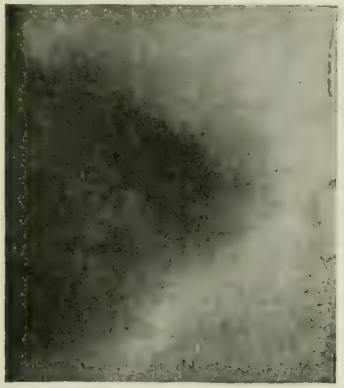


FIG. 12. Reproduction of plate produced by causing a current of air charged with the volatile portions of cedar-wood oil to impinge upon the photographic film: the plate showed no change previous to development.

two fluids examined in test tubes of equal calibre were the same. The amount of acid required was 1·9 cc. Some of this fluid was then preserved in one of the test tubes as the colour control for the future investigations. Acetone extracts of substances 488, 489, 494, and 495 were used, and in each estimation of ionisation 1 cc. of the methyl orange and 2·5 cc. of the acetone extract were diluted with 100 cc. of ammonia-free distilled water. In each case half of the extract was kept in the light, half in darkness.

The results were as follows :—

—	Day 1.	Day 2.	Day 3.	Day 4.	Day 5.
Substance 488 (Light).					
Photographic activity ...	0	0	1	0	2
Basicity	2·6 cc.	2·8 cc.	2·5 cc.	2·65 cc.	2·55 cc.
Substance 488 (Dark).					
Photographic activity ...	0	0	1	0	1
Basicity	2·6 cc.	2·65 cc.	2·65 cc.	2·6 cc.	2·5 cc.
Substance 489 (Light).					
Photographic activity ...	3—4	2	4	0	4
Basicity	2·8 cc.	2·8 cc.	2·55 cc.	2·9 cc.	2·65 cc.
Substance 489 (Dark).					
Photographic activity ...	3—4	2	4	1—2	4
Basicity	2·8 cc.	2·75 cc.	2·95 cc.	2·7 cc.	2·75 cc
Substance 494 (Light).					
Photographic activity ...	1	4	—	—	—
Basicity	2·2 cc.	2·3 cc.	—	—	—
Substance 494 (Dark).					
Photographic activity ...	1	4	—	—	—
Basicity	2·2 cc.	1·9 cc.	—	—	—
Substance 495 (Light).					
Photographic activity ...	2	4	—	—	—
Basicity	2·1 cc.	2·0 cc.	—	—	—
Substance 495 (Dark).					
Photographic activity ...	2	4	—	—	—
Basicity	2·1 cc.	2·0 cc.	—	—	—

These experiments do not appear to lend support to the view that the photographic activity of the extract bears a definite relation to its basicity. Quite apart from the very small differences that were observed from day to day, differences themselves almost within the range of experimental error with so dilute a solution of acid, and hardly to be eliminated by the large number of estimations that were made in each case, there is the greatest irregularity, an increase in photographic activity being noted sometimes with an increase, sometimes with a diminution, of basicity,

and variations of photographic activity occurring with a relative constancy of basicity.*

(13) **Relation of the photographic activity of a substance to the so-called "peroxydase" effect which it produces.**—By the peroxydase effect is meant that blue colouration which is produced in the "guaiacum test" for blood. It depends upon an oxidation of the traces of guaiaconic acid present in the freshly prepared tincture of guaiacum, by oxygen that has been set free from hydrogen peroxide by a substance present in the material which is undergoing the test. The substance which induces this splitting up of hydrogen peroxide has been termed "peroxydase," and it has been regarded by some workers as belonging to the group of the "ferments." Into the question of its nature I shall not enter here, beyond stating that in mode of action and in the ease with which it resists a temperature of 100° C. it differs considerably from the well-known ferments.

In this part of the investigation ether-extracted, dried, and powdered substances and watery extracts have chiefly been used. A few points have, however, been tested on alcoholic and acetone filtrates, and precipitates derived both from the original finely minced substances and from their watery extracts.

The ether-extracted, dried, and powdered substance.—If a number of substances of this description be taken, including both those which produce an effect upon a photographic plate and those which do not, and if portions of these powders be shaken up with distilled water for a short time, a number of yellowish, slightly turbid fluids will be

* The experiments show well, however, the facts that preservation of the extract in the light and in darkness is without influence on the photographic activity, and that the activity of an extract varies from day to day. Daily photographic examination of the same plate affords somewhat similar evidence, but the photographic activity of the small amount of the extract painted on the glass plate ultimately disappears. Thus successive daily re-examinations of the plate made on the first day with the acetone extracts of substances 488 and 489 for the purpose of the experiment detailed above, gave the following values for 488, viz., 0, 2, 0, 0, 0; and for 489, viz., 3-4, 4-6, 2, 1, 2. The plate prepared on the second day gave the values on subsequent days for 488, viz., 0, 0, 0, 0; and for 489, viz., 2, 3, 2, trace. Temporary augmentation of the photographic activity of a substance, or at all events of an extract prepared from it, under what are apparently unaltered conditions, seems to be a definite characteristic of the property.

obtained after the powder has settled. If these fluids be tested for the presence of peroxydase by adding to a small portion a few drops of freshly prepared tincture of guaiacum, and subsequently an excess of a hydrogen peroxide solution, a marked difference will be shown in the results obtained in the different cases. Some of the fluids will have become a deep blue, others will be colourless, while yet others will occupy intermediate positions. By making an arbitrary standard for depth of tint varying between 0 and 6 with watery solutions of methylene blue of increasing strengths, a peroxydase value can be given to a substance which can well be compared with the photographic value to which also arbitrary values varying between 0 and 6 have been given for the purposes of this research. Below are given the results of examination from these two points of view of two series of ten consecutive specimens.

No. ...	220.	221.	222.	223.	224.	225.	226.	227.	228.	229.
Tissue ...	Kidney.	Lung.	Liver.	Kidney.	Lung.	Spleen.	Liver.	Kidney.	Spleen.	Lung.
Photogr. value.	6	4	3	4	2	3	4	2	2	0
Peroxydase value.	0	6+	5	0	4	6+	0	0	4	2

No. ...	320.	321.	322.	323.	324.	325.	326.	327.	328.	329.
Tissue ...	Liver.	Kidney.	Liver.	Kidney.	Liver.	Kidney.	Liver.	Kidney.	Liver.	Kidney.
Photogr. value.	6	3	5	3	5	2	4	2	3	2
Peroxydase value.	2	4	3	5	0	6	1	4	5	6

The foregoing specimens were taken at random and are derived indiscriminately from cases dying with malignant or with non-malignant disease, but they show with sufficient clearness that there is a general tendency for the value of the photographic activity to vary inversely as the peroxydase value. Thus the two cases in which the photographic value was 6 had peroxydase values of 0 and 2; two cases with photographic value 5 had peroxydase values of 3 and 0, while in four cases in which the peroxydase value

was 6 or over the photographic values were 4, 3, 2, and 2; and in each of three cases in which the peroxydase value was 5 the photographic value was 3. It is seen, further, that the tissues in which the peroxydase effect is most pronounced, viz. lung and spleen, are exactly those which a reference to the preceding paper shows are characterised by possessing a very low degree of photographic activity. Similarly, tissues like the liver, and to a less extent the kidney, which affect a photographic plate powerfully, give evidence of a complete absence or a low degree of peroxydase activity.

Below is a series of observations taken from cases of carcinoma.

Tissue	Lung.	Spleen.	Kidney.	Liver.	Primary Growth.	Lymph Gland Growth.	Liver Growth.
C. cervix, F. aged 34.							
Photographic value...	0	0	2	2	2	4	6*
Peroxydase value ...	4	6	0	3	0	0	0
C. cervix, F. aged 47.							
Photographic value...	0	2	2	4	—	—	—
Peroxydase value ...	2	4	?	?	—	—	—
C. sigmoid, F. aged 79.							
Photographic value...	—	—	6	5	—	—	—
Peroxydase value ...	—	—	2	3	—	—	—
C. cervix, F. aged 56.							
Photographic value...	3	1	3	0	5	—	—
Peroxydase value ...	2	5	3	1	0	—	—
C. œsophagus, M. aged 48.							
Photographic value...	—	0	3	2	0	—	—
Peroxydase value ...	—	6+	6−	5	0	—	—
C. breast, F. aged 51.							
Photographic value...	—	—	5	4	5	—	—
Peroxydase value ...	—	—	3	0	0	—	—
C. rectum, F. aged 34.							
Photographic value...	—	—	1	2	—	1	5
Peroxydase value ...	—	—	3	3	—	0	0

* Kidney growth had a photographic value of 1 with no peroxydase value.

Tissue	Lung.	Spleen.	Kidney.	Liver.	Primary Growth.	Lymph Gland Growth.	Liver Growth.
C. cervix, F. aged 52.							
Photographic value...	—	—	3	4	4	—	—
Peroxydase value ...	—	—	1	3	0	—	—
C. breast, F. aged 42.							
Photographic value...	—	—	5	4	3	—	2
Peroxydase value ...	—	—	0	0	0	—	0
C. breast, F. aged 44.							
Photographic value...	—	—	—	2+	—	—	2
Peroxydase value ...	—	—	—	1	—	—	1
C. stomach, M. aged 44.							
Photographic value...	—	—	—	4	—	—	2
Peroxydase value ...	—	—	—	0	—	—	1
C. rectum, F. aged 75.							
Photographic value...	—	—	—	3		4	2
Peroxydase value ...	—	—	—	1	-	0	0
C. tonsil, M. aged 48.							
Photographic value...	—	—	—	2	2	—	3
Peroxydase value ...	—	—	—	? 1	0	—	? 1
C. breast, F. aged 65.							
Photographic value...	0	—	—	—	—	2†	—
Peroxydase value ...	5	—	—	—	—	3†	—

† Lung growth.

From the above it may be concluded that carcinoma tissue, whether primary or secondary, is devoid of peroxydase power even in those instances in which the photographic activity of the tissue is very small. The only noteworthy exception to this statement obtains in the case of the pulmonary metastasis, and here it is likely that some lung tissue with its normally high peroxydase power was included with the carcinomatous tissue itself. Apart from these points there is confirmation of the statement that the photographic and the peroxydase activities of a dried,

ether-extracted, and powdered animal tissue vary inversely as one another.

Below is a series of four cases of sarcoma investigated from the same points of view.

Tissue.	Lung.	Spleen.	Kidney.	Liver.	Pancreas.	Primary Growth.	Lymph Gland Growth.	Liver Growth.	Kidney Growth.	Lung Growth.	Adrenal Growth.	Pancreas Growth.	Thyroid Growth.
S. skin, F. aged 88.													
Photographic value ...	0	1	0	2	1	—	4	3		1	5	3	3
Peroxydase value	5	5	1	5	3	—	3	2	—	3	0	1	0
S. adrenal, M. aged 1.													
Photographic value ...	0	—	2	5	—	3–4	—	—	—	—	—	-	—
Peroxydase value	6	—	2	4	—	5	—	—	—	—	—		—
S. femur, F. aged 22.													
Photographic value ...	0	3	4	3	—	2	—	—	—	—	—	—	—
Peroxydase value	5	4	0	1	—	1	—	—	—	—	—	—	—
S. melanotic, M. aged 63.													
Photographic value ...	0	0	0	4	—	—	5	—	—	—	5	—	—
Peroxydase value	3	4	1	4	—	—	1	—	—	—	2	—	—

Here the case is the same so far as concerns the pulmonary, splenic, renal, and hepatic tissues themselves, photographic and peroxydase activities varying inversely as one another. But a difference is noted with reference to the sarcomatous as compared with the carcinomatous tissue, both primary and secondary; for whereas the carcinomatous tissue shows an absence of peroxydase power, the sarcomatous tissue shows its presence, and sometimes to a considerable degree. So far as they go, these observations indicate that sarcomatous tissue resembles non-sarcomatous in respect of the inverse ratios borne by the photographic and the peroxydase powers to one another.

The observations recorded above suggested so strongly that the manifestation of photographic activity depends upon the absence of peroxydase from the substance to which the photographic plate is being exposed, and conversely that the absence of photographic effect depends upon the presence of peroxydase in the substance, with the corollary that the photographic effect is due to the action of hydrogen peroxide on the photographic plate, and that when peroxydase is

present in the substance any hydrogen peroxide which may be formed is split up at the seat of its formation and never reaches the photographic film at all, that the subject was further investigated. It is clear that the aim was to determine whether the photographic power of a tissue could be caused to disappear by the addition to it of peroxydase, or on the other hand whether a tissue could still give a considerable photographic effect at the same time as it possessed a powerful peroxydase activity. Consideration of the figures given above shows that the absence of photographic power does not necessarily depend upon the presence of a large peroxydase activity, since several instances are given in which both photographic and peroxydase powers were small; in other words, absence of photographic activity may depend upon the absence of a photo-active substance in the tissue under examination, as well as upon a destruction of a potential photo-active substance by peroxydase.

Four powdered substances were chosen: Nos. 17 (with photographic value 6 and peroxydase value 3); 220 (photographic 6, peroxydase 0); 410 (photographic 2, peroxydase 0); and 221 (photographic 0, peroxydase 6+); and the following experiment was made:—(A) One part of each 17, 220, and 410 was mixed with one part of 221 and tested both as regards photographic and peroxydase powers. (B) A strong watery extract of 221 was made and mixed with quantities of each 17, 220, and 410, and the resulting pastes were dried over a water-bath and examined photographically and as regards peroxydase power. The results were as follows:—

Dry.

Substance 17 (Ph. = 6, P = 3) + Substance 221 (Ph. = 0, P. = 6+) gave Ph. value 6, P. value 5.

Substance 220 (Ph. = 6, P = 0) + Substance 221 (Ph. = 0, P. = 6+) gave Ph. value 5, P. value 5.

Substance 410 (Ph. = 2, P = 0) + Substance 221 (Ph. = 0, P. = 6+) gave Ph. value 2, P. value 4.

Mixed Wet and Dried Subsequently.

Substance 17 (Ph. = 6, P = 3) + Watery Extract of Substance 221 (Ph. = 0, P. = 6+) gave Ph. value 4+, P. value 1.

Substance 220 (Ph. = 6, P. = 0) + Watery Extract of Substance 221 (Ph. = 0, P. = 6+) gave Ph. value 4, P. value 0.

Substance 410 (Ph. = 2, P. = 0) + Watery Extract of Substance 221 (Ph. = 0, P. = 6+) gave Ph. value 0, P. value 1.

It appears from this experiment that a dry mixture of a substance possessing strong photographic powers with a substance possessing strong peroxydase powers is without appreciable effect upon either property, but that if moisture be added the peroxydase power is enormously reduced, and the photographic power is diminished though not to a proportionate extent.

Experiments using watery extracts with (a) *photographic and* (b) *peroxydase activities.*—In carrying out experiments to determine the effect of peroxydase upon photographic activity, one of the chief difficulties concerns the properties of the fluids themselves which manifest the peroxydase power. If the peroxydase could be obtained in a pure form, whether as a solid or as a liquid, it would be possible to determine its action with ease. For it would be only necessary to add increasing amounts of a peroxydase solution to a constant quantity of an extract possessing photographic properties, and compare the photographic results of such dilutions with the photographic results of similar dilutions made with water alone. But the peroxydase effect is closely bound up with the protein of an animal solution, and attempts to destroy the peroxydase effect of an albuminous solution generally induce some alteration in the protein content of the solution also. Thus a watery extract of human spleen gives a profound peroxydase reaction, but if one attempts to destroy that reaction with heat one is met by the fact that such a temperature as will, if continued for some time, destroy the peroxydase effect of the fluid itself, is accompanied by a coagulation of the protein, and therefore with a complete alteration of the fluid from other points of view besides the desired one. Moreover there is evidence that the peroxydase property has not actually been destroyed, for examination of the coagulum with guaiacum and peroxide of hydrogen shows that the peroxydase property now resides in the coagulum. A similar result is obtained if the protein be precipitated with alcohol or acetone, for in both these instances, although the filtrate shows an absence of peroxydase power, that power is found to an undiminished extent in the precipitate. In the case of watery extracts of ether-extracted, dried, and powdered substances the difficulty is less, for these fluids have not

the same tendency to throw down a precipitate on boiling, and in them it can be clearly seen that boiling for about thirty minutes entirely destroys the peroxydase power.*

The following courses were therefore adopted :—In one set of experiments the peroxydase factor was represented by the finely divided precipitate thrown down from a watery extract of human spleen. This precipitate had a peroxydase value of 6, and as it had stood under absolute alcohol for several weeks, it was insoluble in water. The reduction in photographic power of the photographing substance used, which was due solely to the addition of the non-photographing precipitate, was represented in the controls by the addition of corresponding quantities of water. In another set of experiments advantage was taken of the fact that albumoses are not coagulated by heat. A watery extract of spleen was made and boiled, and a portion of the coagulum which possessed marked peroxydase power was digested to solution with a preparation of trypsin. The solution showed a peroxydase value of about 5, which was completely destroyed by boiling for half an hour. The loss of water was made up, and varying quantities of the boiled and the unboiled fluids were added to a watery extract of sheep's liver that had been treated with basic lead acetate and sulphuretted hydrogen, and which yielded a photographic effect of value 6. The plates for exposure to the photographic film were prepared in two ways, and for each set of experiments were prepared in duplicate. When the precipitate from the watery extract of

* An idea that seemed to promise well, viz. destruction of the peroxydase in the cold by addition of a small amount of hydrogen peroxide, failed owing to the impossibility of exactly determining the amount of hydrogen peroxide to be added. There is no doubt that if a fluid possessing peroxydase power be subjected to the action of a small quantity of hydrogen peroxide for a short time the peroxydase property disappears. Thus after 15 minutes 2 cc. of a fluid to which 2 drops of hydrogen peroxide have been added has completely lost its peroxydase power, though previously the peroxydase value was 6. The possibility that one might in this way obtain two fluids differing only in peroxydase power (for it was assumed that the peroxydase split up the hydrogen peroxide with the formation of water and the evolution of oxygen gas, and that the increment of water could be balanced by an actual addition of distilled water in the preparation of the control fluid which still possessed peroxydase powers), was negatived in practice by the fact that a strong photographic effect is produced by the presence of traces of hydrogen peroxide too small for detection by other methods. Similarly it was impossible to adopt destruction of the peroxydase by other chemical agents (*e.g.* ammonia) on the grounds that one was thereby introducing another element of uncertainty.

spleen with alcohol was used, drops of the photographing fluid and of the precipitate suspension in water (or of pure water for the controls) were placed on the plate by means of a platinum loop. After all these had been placed in position the sets of drops were mixed, and the resulting large drops were allowed to dry in the air. In the case of the digested watery extract the experiment was combined with one to determine the effect of interaction of the two substances in liquid form for varying times at the body heat. In this case, therefore, the solutions were mixed in bulk in small test-tubes, and small quantities were removed from each test-tube from time to time and placed on the glass plate and dried rapidly in the incubator at 55° C. One of the duplicate plates was used after it had been completely prepared for determination of the peroxydase values of the various mixtures, and a similar determination was made next day on the actual plate that had been exposed to the photographic film. This determination of peroxydase value was easily carried out by adding to the dried drop a minute drop of the guaiacum tincture, and following this immediately with a somewhat larger drop of hydrogen peroxide. These two estimations were necessary to ensure the certainty that the peroxydase effect which was certainly present when the plate was exposed to the photographic film was also present at the end of the experiment. In other words it was necessary in order to determine whether a photographic effect could be produced in the actual presence of a definite peroxydase power.

Below are given the results obtained on a photographic plate which was exposed to a glass plate bearing portions of the mixtures prepared in the first manner described above, along with the composition of the droplets and their peroxydase values before exposure to the photographic film in the incubator at 55° C. for 18 hours.

Composition of Drop. (Ph. = Photographing Substance, P. = Peroxydase Substance.)	Ph. 18–P. 1.	Ph. 24–P. 1.	Ph. 12–P. 1.	Ph. 6 P. 1.	Ph. 3–P. 1.	Ph. 1–P. 1.
Photographic value of mixed drop ...	6	6	6	6	6	6
Peroxydase present (+) or absent (0)	0	0	0	0	0	+
Photographic value of control (H_2O replacing peroxydase)	6	6	6	6	6	6

Composition of Drop. (Ph. = Photographing Substance; P. = Peroxydase Substance.)	Ph. 1-P. 3.	Ph. 1-P. 6.	Ph. 1-P. 12.	Ph. 1-P. 24.	Ph. 1-P. 48.
Photographic value of mixed drop ...	2	1	0	0	0
Peroxydase present (+) or absent (0)	+	+	+	+	+
Photographic value of control (H_2O replacing peroxydase)	3	0	0	0	0

This experiment shows that dilutions of the original photographing substance with the peroxydase material from a strength in which there were 48 parts of photographing to 1 of peroxydase down to one in which photographing and peroxydase substances were present in equal quantities yielded no difference in the photographic value from either the undiluted photographing substance or from dilutions with amounts of water corresponding to the amounts of peroxydase added. Moreover, only the last drop mentioned gave evidence of a peroxydase effect when tested with guaiacum and hydrogen peroxide. When the drop consisted of a mixture in which the peroxydase material preponderated the case was different, for the drop consisting of photographing 1 and peroxydase 3 gave a photographic effect of value 2, whereas the corresponding drop made up with water gave a photographic effect of value 3, and the mixture of photographing 1 and peroxydase 6 had a photographic value of 1, whereas the corresponding drop diluted with water was without effect. Further dilutions, whether with peroxydase material or with water, produced drops entirely without photographic value. Lastly, all the drops in which the peroxydase material was present to, or in a greater proportion than, 1–1 yielded evidence of the presence of active peroxydase by the guaiacum and hydrogen peroxide test.

Below are given reproductions with key diagrams of experiments in which the peroxydase factor was contained in the digested coagulum of a watery human spleen, and in these experiments the effect of keeping the two factors, either separately or mixed in varying proportions, in the incubator at 37° C. for varying lengths of time is considered. In the

first experiment of the series (which throughout consists of dilutions of the photographing substance with 1, 2, 4, 12, or 24 volumes of the peroxydase substance) the two fluids were mixed before placing them in the incubator (Fig. 13), in the

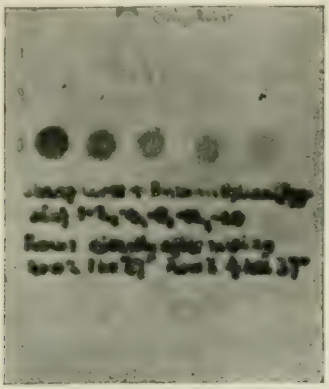


FIG. 13.—Reproduction of plate produced by mixtures of photographing (value 6) and peroxydase substances (value 4) directly after mixing, and after keeping 1 hour and 4 hours in the incubator at 37° C. The peroxydase effect was shown in increasing strengths from right to left in rows 1 and 2, and was absent from row 3, except for a trace in the drop to the extreme right. The writing was done with the same material as was used for the third row of drops. For further details see Text.

second (Fig. 14) the two fluids were kept separately in the incubator for an hour before making the dilutions. In the third (Fig. 15) the fluids were mixed, placed in the incubator at 37° C. for three hours, were then removed, left all night at the room temperature, and next day incubated for varying lengths of time. It is clearly seen on inspecting the vertical columns in the photographic reproductions, and comparing them with the keys, that the photographic value of the droplets in each degree of dilution increases with the length of time that the mixture has remained in the incubator. But, further, a marked difference shows itself according as the substances were, or were not, exposed to a temperature of 37° C. before making the dilutions, and therefore mixing them. For the photographic result is far less marked when the two fluids have been warmed before mixing; another plate taken at the same time, but not here reproduced, showed that the diminution of photographic value is greater when the pre-

liminary warming has been for three hours than when it has lasted for one hour.

The peroxydase values of the droplets were marked at the time when the mixtures were made, but underwent a considerable reduction as the result of exposing the plate to a photographic film for 18 hours in the incubator at 55° C. Thus a

FIG. 14.—Reproduction of plate which has been exposed to mixtures of photographing (value 6) and peroxydase substances (value 4). Substances kept separately for 1 hour at 37° C. and subsequently mixed. Ph. = photographing, P. = peroxydase substance. Peroxydase effect below determined at end of experiment.

—	Ph. 1 vol. P. 1 vol.	Ph. 1 vol. P. 2 vol.	Ph. 1 vol. P. 4 vol.	Ph. 1 vol. P. 12 vol.	Ph. 1 vol. P. 24 vol.	—
Ph. value	1	1	0	0	0	directly after mixing
P. present (+) or absent (0)	0	0	+	+	+	
Ph. value	1	1	0	0	0	after 1 hour at 37° C.
P. present (+) or absent (0)	0	0	+	+	+	
Ph. value	2	>1	<1	0	0	after 2 hours at 37° C.
P. present (+) or absent (0)	0	0	+	+	+	
Ph. value	2	>1	1	0	0	after 3 hours at 37° C.
P. present (+) or absent (0)	0	0	0	+	+	
Ph. value	2	<2	1	0	<1	after 4 hours at 37° C.
P. present (+) or absent (0)	0	0	0	+	+	
Ph. value	2	2	2	0	1	after 5 hours at 37° C.
P. present (+) or absent (0)	0	0	0	+	+	
Ph. value	2	2	2	0	1	after 6 hours at 37° C.
P. present (+) or absent (0)	0	0	0	+	+	

comparison of the peroxydase values before and after exposure to the photographic film becomes less important than direct determination of the peroxydase values of the dried droplets on the plate itself at the end of the photographic exposure. In the first experiment of the series (Fig. 13) there was evidence of peroxydase in all the horizontal rows of droplets, increasing with the amount of the peroxydase that was present in the original dilution: but in this, as in other cases,

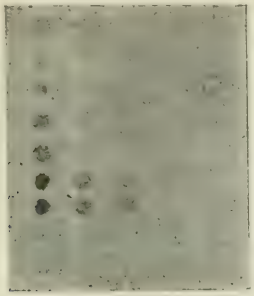


FIG. 15.—Reproduction of plate which has been exposed to mixtures of photographing (value 6) and peroxydase (value 4) substances. Substances mixed in cold and subsequently exposed to warmth for 3 hours. Ph. = photographing, P. = peroxydase substance. Peroxydase effect below determined at end of experiment.

—	Ph. 1 vol. P. 1 vol.	Ph. 1 vol. P. 2 vol.	Ph. 1 vol. P. 4 vol.	Ph. 1 vol. P. 12 vol.	Ph. 1 vol. P. 24 vol.	—
Ph. value	2	1	?	0	0	} 3 hours.
P. present (+) or absent (0)	0	0	+	+	+	} after mixing
Ph. value	3	2	1	0	0	} after 4 hours
P. present (+) or absent (0)	0	0	+	+	+	} at 37° C.
Ph. value	3	2	1	0	stuck	} after 5 hours
P. present (+) or absent (0)	0	0	+	+	+	} at 37° C.
Ph. value	4	2	1	0	stuck	} after 6 hours
P. present (+) or absent (0)	0	0	0	+	—	} at 37° C.
Ph. value	4	3	2	?	?	} after 7 hours
P. present (+) or absent (0)	0	0	0	+	—	} at 37° C.
Ph. value	6	4	3	1	1	} after 8 hours
P. present (+) or absent (0)	0	0	0	+	—	} at 37° C.
Ph. value	6	4	4	1	2	} after 9 hours
P. present (+) or absent (0)	0	0	0	+	—	} at 37° C.

the dried drops that gave the guaiacum test were those in which one part of the photographing substance was mixed with four parts or more of the peroxydase substance; with less than four parts no evidence of peroxydase was given. In the last two experiments (Figs. 14 and 15) peroxydase effect was manifested by the dried drops constituting parts of the third, and the whole of the fourth, and of the fifth, vertical columns. That is to say, the peroxydase effect was manifested in drops that contained four or more parts of the peroxydase substance to one of the photographing. With dilutions in which less than four parts of the peroxydase substance were present, and in those in which, although four parts of the peroxydase substance to one of photographing were present, the mixture had been exposed to the action of a temperature of 37° C. for three or more hours, the peroxydase effect was completely lost.

From these experiments it must be concluded that the diminution of photographic effect when the photographing substance is diluted with a peroxydase substance is greater than it is when the dilution is effected with water alone; that a much greater diminution of photographic effect is brought about by allowing the photographing and the peroxydase substances to be acted on separately by a temperature of 37° C. than by mixing them directly; and that under either of these circumstances prolonged exposure to a temperature of 37° C. leads to a progressive intensification of the photographic, and a corresponding diminution of the peroxydase, effect.

Examination of the photographing and the peroxydase substances individually shows that the difference in effect between warming the fluids before mixing and mixing them unwarmed depends upon the peroxydase factor. For, whereas the photographic value of the photographing substance undergoes no diminution as the result of exposure for three hours to a temperature of 37° C., such an exposure of the peroxydase substance leads to a considerable increase of the depth of blueness produced on the addition of tincture of guaiacum and hydrogen peroxide. On the other hand it is clear that the peroxydase substance *when in the presence of the photographing substance* is progressively destroyed by the action of a temperature of 37° C., and allows the photo-

graphing property to manifest itself anew. Whether the actual increase in photographic value produced by exposure of the drop containing both photographic and peroxydase substances to a temperature of 37° C. for three or more hours is due to an intensification of the photographic substance itself, or to an unmasking of a photographic substance in the peroxydase substance owing to the destruction of the peroxydase, or to a conversion of the peroxydase into a photographing substance, it is impossible to say at present with certainty. Evidence, however, has already been given to show that the development of photographic power in a watery fluid giving no peroxydase reaction can be aided by the action of heat.

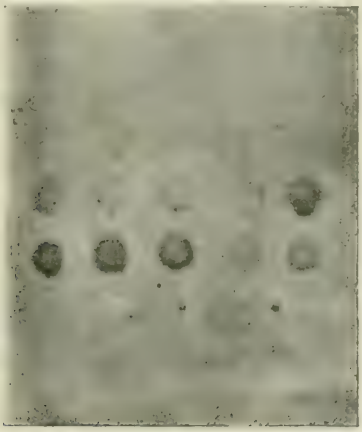


FIG. 16.—Reproduction of plate which has been exposed to mixtures of photographing (value 6) and peroxydase (value 4) substances. Peroxydase effect below determined at end of experiment. Ph. = photographing, P. = peroxydase substance.

—	Ph. 1 vol. P. 1 vol.	Ph. 1 vol. P. 2 vol.	Ph. 1 vol. P. 4 vol.	Ph. 1 vol. P. 12 vol.	Ph. 1 vol. P. 24 vol.	
Ph. value	2	1	1	2	0	directly after mixing
P. present (+) or absent (0)	+	+	+	+	+	
Ph. value	2	2	2	0	0	after 1 hour at 37° C.
P. present (+) or absent (0)	0	0	+	+	+	
Ph. value	3	3	3	2	5	after 2 hours at 37° C.
P. present (+) or absent (0)	0	0	+	+	+	
Ph. value	6	6	6	3	5	after 3 hours at 37° C.
P. present (+) or absent (0)	0	0	+	+	+	

In addition to the points which have been noted above, it is important to recognise that, although there is evidence of a marked inverse ratio between the photographic and the peroxydase values, there is clear evidence that a dried drop which manifests a considerable peroxydase effect, not only before, but also at the end of an exposure to a photographic film, is able to produce a photographic effect. This is shown in some degree in each of the experiments given above, and especially in the case of those dilutions which were acted on by a temperature of 37° C. for a period of three hours or more. In the experiment of which Fig. 16 is a reproduction the last three results of the last two rows, having photographic results of 3, 2, and 5, and 6, 3, and 5, respectively, were produced by drops that showed a marked peroxydase value, even at the end of the exposure to the photographic film.

In the following experiment the part played by peroxydase was tested by using two otherwise similar fluids which differed in the amounts of peroxydase effect they produced, No. 81 giving an intense blue with the guaiacum test, and No. 97 giving practically no blue colour at all.

Comparison of the photographic effects with the peroxydase effects as given in the key shows that the same photographic substance yields a photographic image of value 1 when the peroxydase values are 3 and 1, and after warming for two hours it gives photographic images of value 2 or over when the peroxydase values are 2 and 0. The same degree of photographic effect is here produced by two materials differing considerably in peroxydase value.

In connection with this subject it is noteworthy that substances which when dried and powdered yield no photographic effect may do so in respect of their watery or acetone extracts. This has been observed in the case of several samples of spleen. The point is not yet worked out, but it is possible that the result may be due to the fact that spleen possesses a small quantity of the photographing substance which is concentrated in the extract. It may be, also, that the photographic activity of the dried powdered substance is masked by the large amount of peroxydase activity which it possesses. In any case the photographic activity of the extract is much less than that of extracts of substances which yield photo-

FIG. 17.—Reproduction of plate which was exposed to mixtures of photographing (value 6) and peroxydase substances 81 and 97 (values 6 and 70 respectively). Peroxydase values below determined at end of experiment.

First Horizontal Line.

—	81	Ph.	97	—
Ph. value	< 1	6	< 1	before experiment
P. value	3	0	70	

Second and Third Horizontal Lines.

—	Ph. 1 vol. P. 1 vol.	Ph. 1 vol. P. 6 vol.	Ph. 1 vol. P. 12 vol.	Ph. 1 vol. P. 24 vol.	—
Subst. 81 Ph. value ...	4	2	1	1	directly after mixing
Subst. 81 P. value	1	3	3	3+	
Subst. 97 Ph. value ...	5	4	1	1	
Subst. 97 P. value	0	0	?	1	

Fourth Horizontal Line.

—	81	Ph.	97	
Ph. value	< 1	6	< 1	after 2 hours at 37° C. separately
P. value	4	0	0	

Fifth and Sixth Horizontal Lines.

—	Ph. 1 vol. P. 1 vol.	Ph. 1 vol. P. 6 vol.	Ph. 1 vol. P. 12 vol.	Ph. 1 vol. P. 24 vol.	
Subst. 81 Ph. value	6	4	3	2	after 2 hours at 37 C. mixed
Subst. 81 P. value ...	0	0	2	2	
Subst. 97 Ph. value ...	6	5	2	2	
Subst. 97 P. value	0	0	0	0	

graphic results in the dried and powdered condition. (Cf. Fig. 5.)

(14) **The Action of Calcium Chloride** (cf. Figs. 9 and 11).— The effects of shaking up an acetone extract of a finely-divided liver with a large excess of calcium chloride and similar treatment of an acetone extract *of a watery extract* of the same liver are very different so far as concerns the photographic value of the dehydrated fluids when they are examined photographically. For whereas the acetone-calcium chloride fluid gives a profound effect photographically, the water-acetone-calcium chloride fluid is entirely without effect. This is shown by the following instances :—

Number.	Nature of Extract.	Photographic Value of Extract.
426 ...	AcE, $CaCl_2$	6
	WE, AcE, $CaCl_2$ ...	0
429 ...	AcE, $CaCl_2$	5
	WE, AcE, $CaCl_2$ ...	0
431 ...	AcE, $CaCl_2$	5
	WE, AcE, $CaCl_2$ ...	0
435 ...	AcE, $CaCl_2$	?
	WE, AcE, $CaCl_2$ ...	0
437 ...	AcE, $CaCl_2$	6
	WE, AcE, $CaCl_2$ ...	0
439 ...	AcE, $CaCl_2$	3
	WE, AcE, $CaCl_2$ ...	0

The difference between a direct acetone extract and an acetone extract of a watery extract (e.g. of liver) lies in the fact that the acetone extract made from the liver direct contains all such substances of the liver as are alone soluble in acetone or in a strong watery solution of acetone. The watery extract of the liver on the other hand entirely eliminates these very substances, and the acetone extract of the watery extract only contains those substances of the liver which are soluble in water or in acetone or in mixtures of the two. With fair accuracy, therefore, one may regard the two extracts as respectively containing the acetone-soluble and the acetone and water-soluble substances of the liver, free from protein. Further, dehydration with $CaCl_2$ must throw out of solution those substances in the watery extract which are soluble in water alone or in all but the strongest acetone; and the same

is true for the direct acetone extract, with the modification that those substances have largely been excluded by the large amount of acetone added to the finely-minced liver in order to prepare the acetone extract. But the acetone extract of a watery extract yields definite photographic results, and the difference between the absence of photographic effect of an acetone extract of a watery extract treated with $CaCl_2$ as compared with the great effect of a direct acetone extract treated with $CaCl_2$ can only mean that the removal of water has at the same time removed a photographing substance. And since the same treatment of the direct acetone extract leaves a fluid which exerts profound photographic effects it must be concluded that at least two substances are present in the liver capable of affecting a photographic plate, one of which is soluble in water and the other in acetone.

Results similar to those described above were obtained in two samples of carcinomatous metastasis derived from a case of carcinoma of the rectum; but in two metastases from a case of carcinoma of the breast, and in a sample of human muscle, no photographic result was obtained with either of the extracts treated with $CaCl_2$.

(15) **The Pigmentary Constituents of the Tissues.**—These may be dismissed shortly. In the case of almost all the tissues employed for the research watery and ethereal extracts yielded yellow pigments. Though the colour was the same there is no doubt that two pigments at least were present, one being soluble in water and entirely insoluble in ether, chloroform, benzene, ligroin, and xylol, and the other being soluble in these substances and completely insoluble in water. The effect of the pigment was investigated by examining fluids before and after removal of the colouring matter with specially prepared animal charcoal (itself without effect upon the photographic plate). No difference whatever in the behaviour of the coloured and the colourless fluids was recognisable, and the charcoal used for decolourisation was itself without effect upon the film.

(16) **The Effect of Protein in the Extracts.**—The fact that a watery extract unheated or only heated to 37° C. frequently

yields no photographic effect, while the same extract heated to 100° C. may produce a considerable effect, has already been mentioned, and it has been pointed out that such peculiarity of a watery extract is not shared by an acetone extract. From this it would appear that the peculiarity is due to the presence of protein in the watery extract prepared at lower temperatures and removed by coagulation in the case of the watery extract heated to 100° C. and precipitated by the acetone in preparation of the acetone extract. The question is, however, complicated by the peroxydase activity shown by the coagulum or precipitate and by the watery extract prepared at lower temperatures. Use was therefore made of egg-white, which yields only a slight peroxydase

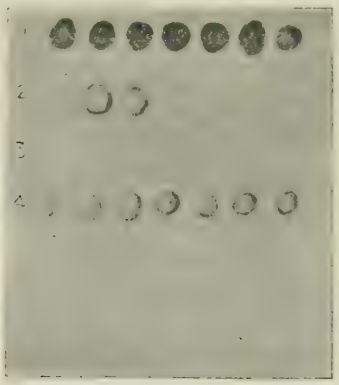


FIG. 18.—Reproduction of plate showing that protein in the absence of peroxydase does not diminish the photographic value of a substance. Row 1 = drops of the original photographing substance; row 2 = drops of the photographing substance diluted with an equal quantity of distilled water; Row 3 = drops of the 1–1 egg-white water solution; row 4 = drops of the photographing substance diluted with an equal quantity of egg-white solution.

reaction even in concentrated solutions, and in the sample used was entirely without peroxydase reaction. A watery extract of sheep's liver was taken, of which the photographic value was 6. Equal quantities of this extract were mixed with equal quantities of a concentrated solution of egg-white (1–1) on the one hand and distilled water on the other. Drops were then placed on a glass plate and dried in the incubator at 55° C. They were then exposed to a photo-

graphic plate in the usual way. The results were as follows: The original photographing substance gave a photographic result of value 6, the mixture of photographing substance and water in equal parts gave a result of values varying between 1 and 4, while the mixture of photographing substance and egg-white solution in equal parts gave a similar or slightly more intense result. The egg-white solution itself was without photographic effect. A reproduction of the actual plate is given in Fig. 18.

GENERAL CONSIDERATION OF RESULTS.

In the main the information afforded by the experiments detailed in the preceding pages is of a negative kind, dissociating the photographic property from a variety of materials, but not indicating its precise nature. It is clear that the property is not one of protein, of fat, of cells, of pigment or of blood, as such, while the absence of photographic effect from the incinerated ash shows that the inorganic constituents (or at least such of them as are not volatilised by the heat) are not the cause. There is, however, evidence that the property is bound up in some way with the non-crystallisable organic constituents, that it can resist a considerable degree of heat, and, although it rapidly disappears when exposed to air, is not volatile. There is evidence, too, that the photographic effect is produced by at least two substances present in the liver, one of which is soluble in water, the other in acetone. It is differentiated from the photographic property of recognised radio-active substances by the fact that animal substances cannot exert a photographic effect through a sheet of mica. On the other hand an effect is produced when a thin layer of celloidin has been painted over the substance even when that layer of celloidin is many days old, but there is doubt whether this can be compared with the action that takes place through mica in the case of a true radio-active substance. Whether the photographic activity of an animal tissue is comparable with the action of the α-radiations of radio-active substances it is impossible to say.

It is equally difficult to determine whether the photographic effect is intrinsically due to the action of hydrogen

peroxide liberated from the animal substance as has been suggested by Russell. The close inter-relationship which exists between the photographic power and the so-called peroxydase power seems to point in this direction. For if hydrogen peroxide be formed in an animal substance and produce an effect on a photographic plate, the presence in that substance of a material which splits up hydrogen peroxide as fast as it is made must result in a complete absence of photographic effect. Against this view is the undoubted fact that substances may produce a profound photographic effect at the very time when they are exerting a considerable peroxydase effect. Again, the effect of keeping mixtures of photographing and peroxydase substances in the incubator for some hours seems to indicate that the photographic property is only masked by the presence of peroxydase, and is not destroyed. In some measure, too, the fact that the substances can produce a photographic effect at a temperature of 100° C. in dry air is evidence against the view that the photographic action is due to hydrogen peroxide, since it is not easy to understand how dissociation would not occur under these circumstances. In this connection the experiments of Dr. Colwell are of importance, for he shows that when pure cholesterin is exposed to the vapour of hydrogen peroxide the effect on the photographic plate, which is at first intense, passes off very rapidly, and in the second place he shows that a photographic effect is produced by substances that have remained unaltered, so far as can be told, for indefinitely long periods. Even if we exclude the case of the prehistoric calculus on the ground that the photographic result obtained is very small, we find difficulty in accepting the view that the small amount of organic material in the calculus known to be 120 years old has been giving off hydrogen peroxide for that length of time and is still continuing to do so.

In many ways similar to the effect shown by Russell to reside in woods, the photographic effect manifested by certain animal substances differs in respect of the fact that, unlike wood, it is uninfluenced by the action of light and darkness, and, taking cedar-wood oil as an example of the substance upon which the action of wood depends, the photographic property of animal tissues differs from that residing in woods

by the fact that the substance exerting photographic power can be carried over by a current of air in the case of woods, but cannot be so carried over in the case of animal tissues.

So far, then, as these experiments go they indicate that the photographic property possessed by certain animal tissues differs from the photographic properties manifested by recognised radio-active substances on the one hand, and substances such as wood on the other. Nevertheless, in respect of the photographic property these animal tissues have affinities with both varieties of substance.

CONTRIBUTION TO THE STUDY OF X-RAY CARCINOMA AND THE CONDITIONS WHICH PRECEDE ITS ONSET.

(First Communication.)

By CECIL W. ROWNTREE.

It is a well-established fact that prolonged exposure to the X-rays in numerous instances has resulted in the production of a new growth, which in microscopic appearance is indistinguishable from squamous cell carcinoma. In certain of the cases, amputation of individual fingers, or of the whole limb, has been necessary, in others metastatic growth has occurred and proved fatal.

So far as it has been possible to determine, there have been in Great Britain since 1896, when Röntgen rays were first extensively experimented with, seven cases of X-ray carcinoma, and of these it appears that up to the present time one has proved fatal.

All the cases have arisen in either the medical men or their assistants and nurses who utilise the rays for therapeutic or skiagraphic purposes, or in the mechanics who in the process of manufacturing apparatus are constantly exposed to the influence of the rays.

In addition to the above cases, there are of course many in which grave pathological conditions short of carcinoma have developed, not only in the classes of individuals already enumerated, but in large numbers of patients who, either in the process of skiagraphy, or during the treatment of such conditions as ringworm, rodent ulcer, or lupus, have suffered over-exposure.

In the case of lupus also it appears certain that since the introduction of X-ray treatment the percentage of cases in which the lupoid ulcer has become carcinomatous has very materially increased, although it is of course impossible in

any given case to form an estimate as to whether carcinoma would have supervened had some other method of treatment been adopted. This point will be referred to later.

By the courtesy of Mr. Pearce Gould, Mr. Foulerton, Mr. Kellock, and Mr. Dean, it has been possible to obtain specimens of five cases of carcinoma arising in X-ray workers, and the present paper is founded on the examination of this material, and also upon investigations carried out on patients in the cancer wards of the Middlesex Hospital.

It is proposed in this preliminary communication to give brief accounts of the clinical history and histological character of the cases of carcinoma, and then to consider the changes induced in normal skin by the application of X-rays for varying periods, with the hope that some light may be thrown upon the conditions which underlie the production of carcinoma in these cases.

There appears to be a doubt in the minds of some observers as to whether the new growth in these and similar cases is in reality carcinoma. Examination of the specimens upon which this paper is founded leaves no difficulty in accepting them as examples of typical squamous cell carcinoma. In this connection de Beurman, who has studied an example of the condition, says: "l'identité clinique et histologique absolue avec les cancers cutanés à type d'épithélioma pavimenteux lobulé est un fait incontestable."

Below is an account of the clinical histories of the cases.

CASE I.

This case is described first because it was the most advanced of the series, owing to the fact that the patient deferred for a long period the amputation which his medical advisers had recommended. At the time of operation he was 42 years of age, and had for several years been engaged in the manufacture of X-ray apparatus. For two years the left hand had been affected, and eighteen months previously a growth had appeared on the middle finger.

He refused to see a surgeon for some time, and when ultimately he did so, it was found that the left middle finger was very greatly enlarged by an irregularly lobed new growth,

which was ulcerating on the surface and very foul. The skin on the dorsum of the hand and remaining fingers was thin and atrophic, and there were also numbers of irregular pigmented warts. No enlarged glands were detected either at the elbow or in the axilla. The finger was amputated through the proximal end of the shaft of the third metacarpal bone, and the patient made a good recovery.

Since the operation, which was in 1905, the condition of the hands has remained more or less stationary, but severe burns have developed on the chin and upon the chest. There is an ulcer upon the chin which refuses to heal, its exciting cause being apparently a razor cut; while upon the chest is an ulcerated condition which is very definitely confined to the area represented by the opening of the waistcoat.

The amputated finger proved to be of very great interest. A skiagram was taken, and is shown in the accompanying illustration.

The total disappearance of the bony tissue of the first and second phalanges will be noted as a remarkable feature, such complete destruction being an unusual occurrence in invasion of bone by carcinoma. The appearance of this skiagram led to further investigation of the condition of the bones after prolonged exposure to X-rays, and the results will be detailed later.

Microscopic examination of the growth shows that it is composed of small and slender columns and islets of squamous cells, irregularly distributed and separated from one another by a well-marked connective tissue stroma composed of large cells with large nuclei. There is slight keratinisation, but there are no well-formed cell nests. Many of the epithelial cells, and also certain of the connective tissue cells, show mitotic figures; but the tissue was not obtained sufficiently early after removal to render it possible accurately to determine the number of chromosomes present in the nuclear figures.

Of special interest in this specimen is the striking appearance of the connective tissue stroma, the individual cells being of a size and character not usually met with. Their large size and great number produce an appearance as if the small islets of epithelial cells were dispersed throughout

FIG. 1.—Skiagram of the finger removed in Case I. Note the total disappearance of the bony tissue of the second and third phalanges and their replacement by a bulbous mass of growth.

granulation tissue, and suggest the view that the connective tissue cells themselves are endowed in these instances with a special activity. None of the cells was found to be multinucleated.

CASE II.

This patient, when seen in July 1905, was 38 years of age, and had been working with X-rays for six years. He had chiefly experimented with the manufacture of Cossor tubes, but owing to trouble with his hand, gave up this work in 1902. Examination showed that the skin of both hands was thin and glossy and much pigmented, while punctate dilated vessels were thickly studded over the dorsum of hands and fingers.

On the dorsum of the proximal phalanx of the right middle finger was an ulcer 1 in. in diameter with slightly raised and rolled edges, fixed to the underlying structures and with a soft base of pinkish colour and irregular surface. This ulcer was steadily growing.

Over the dorsum of the third metacarpal bone was a small ulcer, somewhat raised above the surface, over which a thin scab formed from time to time; while on the back of the carpus was a similar ulcer one-third of an inch in diameter. Neither of these ulcers showed any signs of healing. There were no enlarged glands to be felt, either at the elbow or in the axilla.

The finger was amputated with nearly the whole metacarpal bone and the ulcer over it. The patch over the carpus was also excised and the wound grafted.

The patient remained well for one year, at the expiration of which a small ulcer appeared over the proximal end of the third metacarpal bone, just at the upper end of the scar of the first operation. It persisted for some weeks, but eventually healed, leaving a scar. A few months later, however, a scab formed over this scar, and was gradually raised and thrown off, disclosing a prominent growth which rose dome-like above the skin, the size of half a cherry. It was of bright red colour, firm consistency, and was freely movable over the underlying structures. There was no glandular enlargement, and the remainder of the hand showed consider-

able improvement on its former condition. As this growth showed no signs of healing it was removed, and the resulting wound covered with a Thiersch graft.

There has been no recurrence of any kind since that date, but there has been little or no improvement in the general condition of the man's hands, which are in very much the same state now (May 1908) as they were three years ago.

The finger of this patient is preserved in the Museum of the Royal College of Surgeons (4086c), and shows on the dorsum a shallow ulcer, which has by no means the typical appearance of a malignant growth. The base is clean and smooth, and the edges merge somewhat gradually into the surrounding healthy tissues.

However, a section across the ulcer shows that the growth has extended into the tissues of the finger for a depth of one-fifth of an inch, and invaded the dorsal tendon sheath.

Microscopic examination of the growth reveals a keratinising squamous cell carcinoma in which the cell nests are numerous and well developed. The stroma of the growth has no peculiar characteristics, and there is nothing that calls for special notice. Examination of the tissue beyond the edge of the ulcer has not been possible, and nothing therefore can be said about the condition of the subepithelial tissues in the neighbouring skin.

The recurrent growth was of greater interest. It will be remembered that clinically it formed a dome-like swelling sharply defined from the surrounding skin. Microscopic examination shows no new growth, the mass consisting entirely of young granulation tissue, which entirely replaces epidermis and corium over a limited area, the epidermis gradually merging into and disappearing in the granulation tissue mass. Examination of the granulation tissue shows that the cells composing it are unusually large and well developed, and possess large round or oval nuclei containing much chromatin and staining deeply. In fact the appearance of these cells is strikingly similar to that of the cells which form the stroma of the new growth in Case I.

In the skin beyond the edge of this granulation tissue mass there are slight changes which are most marked in the elastic tissue. This has disappeared in a narrow zone below

the epithelium, just as is shown in Figs. 11 and 15 in Dr. Bonney's paper (this vol., pp. 47 and 51). A moderate number of plasma cells is present in the de-elasticised area.

CASE III.

The early history of this case has already been reported by Mr. Foulerton in the "Transactions of the Pathological Society," vol. 56, and is briefly as follows:—

The patient began work with X-rays in 1897 at the age of 38. In 1899 he noticed loss of tactile sensation in the fingers of both hands, at the same time the skin of the dorsum of the hand became dry and scaly, the hair fell out, and the nails became hard and brittle. In May 1903 a severe attack of dermatitis followed a single prolonged exposure to the rays; the left hand suffered particularly, the skin on the dorsal aspect of the first, second, and third fingers being severely blistered. The resulting ulcers took four months to heal, the new skin being thin and tender, and showing numerous nævoid petechiæ. The nails were shed, and the new ones replacing them grew slowly and irregularly. Warty patches next developed on the dorsal aspect of the middle phalanges of the index and the second fingers.

A second and similar attack followed another single long application of the rays in December 1903. The skin on the dorsal aspect of the first and second fingers was again blistered, and a small ulcer over the middle phalanx of each of these fingers again resulted. The ulcer on the index refused to heal, and became the seat of pain, which was especially severe at night-time. In February 1904 a saturated solution of potassium permanganate was applied to the ulcer, which during the next two months showed some signs of healing, but in May all attempts at healing ceased, and the ulcer gradually increased in area and depth. In September 1904 the finger was amputated. Two years after the amputation there was still a small superficial ulcer on the dorsal aspect of the middle phalanx of the second finger of the same hand, and as this refused to heal, it was excised, and the surface grafted.

Histological appearances of the new growth on the index finger.—The new growth is composed of columns of squamous cells which are growing freely into the substance of the corium, while at one point the underlying bone has been invaded by the growth. The keratinisation is well marked, and cell nest formation frequent and conspicuous.

The second portion of tissue removed shows irregular thickening of the surface epithelium, which shows a tendency to early keratinisation. There is a considerable number of lymphocytes and leucocytes lying in the prickle spaces between the deeper cells, but otherwise there is nothing abnormal in this layer. The elastic tissue has disappeared in a narrow zone below the epithelium, and its place is taken by a moderate number of plasma cells and lymphocytes.

The specimen is therefore not actually malignant, but is exactly similar to many of the "pre-cancerous" conditions illustrated in Dr. Bonney's paper, with the exception that the plasma cell infiltration is less well marked (cf. Fig. 15, p. 51).

CASE IV.

This patient was a man aged 60, who had been engaged in the manufacture of X-ray tubes for some years. Some time previously a small painful crack had appeared over the last interphalangeal joint of the first finger. This crack had gradually increased in size until at the time of examination it appeared possible that a new growth was commencing, and the affected area was accordingly excised.

There has been no recurrence, and at the present time (May 1908) the condition of the hands—never very bad—has slightly improved.

Microscopic examination of the tissue removed reveals the existence of an early, but undoubted, squamous cell carcinoma. At the edge of the growth there is great thickening of the horny layer of the epidermis, and there are many granules present in the superficial layers of prickle cells. The growth shows a slight tendency to the formation of cell nests. There is a slight cloud of cell infiltration, including plasma cells, in the subepithelial tissues, which have a hyaline appearance, and do not stain well.

CASE V.

In this case—that of a man aged 40—the third finger was amputated at the metacarpo-phalangeal joint, and the metacarpal bone dissected out subsequently.

The axillary tissues were also dissected out, owing to the fact that the lymphatic glands were enlarged. Examination of the mass of axillary tissue revealed the fact that there were three or four glands present, one of which was obviously larger and firmer than usual; but there was no evidence that they were the seat of new growth, either to the naked eye, or on microscopic examination.

The skin of the amputated finger had a glazed appearance, and was thin and adherent to the underlying structures. The nail had entirely disappeared except for a small portion at one edge; while the nail bed had flattened down, and its surface was similar in appearance to the neighbouring skin. There was nowhere any actual ulceration, nor were there any cracks or warts. But at the base of the finger was an area where the surface epithelium showed a slight irregularity of surface, but no obvious ulcer. However, sections taken through the thickness of the skin at this spot showed the presence of a malignant growth infiltrating the deeper structures, which had all the ordinary characteristics of a typical squamous cell carcinoma, cell nest formation being well marked.

The microscopic appearances of the remainder of this finger will be referred to later under X-ray dermatitis.

Consideration of these cases brings out the following points:—

1°. The early age at which these patients were attacked; the average age for the occurrence of carcinoma of the hand under ordinary circumstances is much later.

2°. The essential similarity of the causative factor; prolonged and frequent exposure to the emanations from tubes of all varieties of make and intensity. So varied have these been that it is impossible to form any opinion as to whether any particular type of tube has greater influence than any other.

3°. The long duration of what may be termed the pre-cancerous stage—the stage of chronic dermatitis—the atrophic

and hypertrophic changes which precede the malignant process.

4°. The slow and insensible gradation from these pre-cancerous conditions to undoubted malignancy.

5°. The progressive nature of the pathological change when once established; for in several instances it has happened that carcinoma has supervened after a period of varying length, during which no exposure has taken place.

6°. The low degree of malignancy of the growth: for in none of the above cases was there metastasis in the lymphatic glands, and in none has there been up to the present time any recurrence of the growth.

X-RAY DERMATITIS.

Short of malignant disease the pathological changes summed up in the comprehensive term X-ray Dermatitis—although the change is far from being dermatitis in the ordinary acceptance of the word—have been studied by the examination of portions of skin removed from patients who have had prolonged exposures for the treatment of various conditions; by the examination of the non-malignant portions of the fingers removed in the cases already described, and by the investigation of the results of exposing rats to the rays.

The clinical appearances of the disease in its advanced stages are now well known; the telangiectases, the irregular nails, and the thin atrophic wart-bearing skin are familiar to all interested in X-ray work.

The best description of the clinical features of the condition is that given by Dr. Hall Edwards, who has himself suffered severely. He says "the disease, so far as the hands are concerned, makes its first appearance as an erythema round the base of the nails. The erythema gradually becomes more marked, and transverse and longitudinal ridges form on the nails, which become excessively brittle, and exhibit a tendency to separate from the matrix. They gradually thicken, their substance degenerates, and they ultimately become shapeless masses. The skin becomes uniformly red, and later small warty growths appear, which gradually

increase in size and number, the skin at the same time becoming dry and wrinkled. At this stage the patient suffers but little pain, but the warty growths increase in size, especially over the knuckles, with the result that the skin cracks on the slightest extra exertion. These cracks are extremely painful, and very slow to heal. There is great pain, which is aggravated by holding the hands in a dependent position, and apparently originating in the bones. There is at the same time a certain amount of loss of power in the muscles of the arm. Later the skin shows marked telangiectasis, and becomes considerably thickened and tied down to the subjacent tissues. The bases of some of the large warts become inflamed, and the thickened mass comes away, leaving an ulcer which takes months to heal, and is so painful and so tender that words fail to convey any idea of the constant suffering which results. It is ulcers of this type which occasionally entirely refuse to heal, become gradually larger, and assume malignant characters."

An interesting point in the above description is the statement that much of the severe pain felt appears to arise in the bones. When it is remembered that many of the cases exhibit very marked alterations in the bones, as shown by the skiagraphic shadows, it would seem probable that this pain may be regarded as an indication of the profound changes these structures are undergoing.

The first case of X-ray dermatitis is one in which it was possible to obtain for examination one of the warts already described before any ulceration had occurred.

The patient was a man who commenced work as an X-ray operator in 1901, and has been exposed to the rays daily ever since.

After working for three years the hands and fingers began to suffer, and considerable pain was felt, especially in connection with a small wart on the dorsal aspect of the first phalanx of the right index finger. The hands slowly became worse, the wart on the finger progressively increased in size, and six years after commencing work the pain became so severe that the wart was removed.

Pain disappeared on the removal of the wart, but the rest of the hand remained very tender, so tender that even now

he is unable to shake hands without suffering considerable discomfort.

During the last three years this patient has been careful to protect his hands from the influence of the rays, and while there has been no marked improvement, on the other hand there has been no alteration for the worse.

Microscopic examination of the portion of tissue removed shows irregular overgrowth of the epidermis resulting in the production of a flat-topped papilloma.

In the centre of the growth the papillary arrangement of the epidermis has disappeared, the level of the lowest layer of epithelial cells being the same as that of the lowest part of the interpapillary processes of the epithelium on either side, which also show irregularity.

There is no actual epithelial invasion of the corium, but the deeper layers of cells are more irregularly arranged than is normally the case, and there is a tendency to unduly early keratinisation.

Specimens stained by Weigert's method show that there is loss of the underlying elastic tissue, and Bonney's stain shows that its place is taken by a moderate infiltration of lymphocytes and plasma cells.

The irregularity of the epithelium, the disappearance of the elastic tissue, and the plasma cell infiltration, would appear to indicate that this wart was removed none too soon, and that, although not definitely carcinomatous, it may be regarded as being extremely close to the border line of malignancy.

The next specimen to be described is of special interest, as it was obtained from the scalp of a patient who, during the treatment of an inoperable sarcoma of the neck, had had many exposures to the rays, which had resulted in the production on the scalp just behind the ear of an area of X-ray dermatitis severe enough to cause loss of nearly all the hair and to produce a thin, glazed, and atrophic condition of the skin.

For purposes of comparison a piece of scalp was removed from the corresponding position on the head of a bald old man.

Microscopic examination of these two specimens shows thinning of the epidermis in each case, but no material altera-

tion in the epithelial cells themselves. Hair follicles are very sparsely scattered in each case, but whereas in the case of the naturally bald scalp the remaining follicles are normal in appearance and stain well, the follicles in the other specimen —the irradiated skin—are in some cases merely represented by masses of degenerate material showing no cellular structure; in others, where their epithelial structure appears to be intact, the connective tissue surrounding them shows a condensation and staining quality which is not normal.

Differential staining reveals the presence of an excess of elastic tissue round these follicles, and a disappearance in a narrow zone under the epidermis. The significance of the changes will be discussed later, and the various changes which occur in the minute structure of the skin will now be described in detail.

They will be considered under the following headings—

The epidermis.
The elastic tissue.
The epithelial appendages.
The connective tissue, bones, vessels, and nerves.

Changes in the Epidermis.—In the early stage of X-ray dermatitis, the epidermis appears to undergo hypertrophic change, it becomes thickened, and the presence of a number of mitotic figures, not only in the basal cells but also in the more superficial cells—where normally mitotic figures are rarely seen—is evidence of an unusual cell activity.

At a later stage this state of affairs is replaced by an atrophic change, the epithelium becoming much thinner, the papillæ disappearing and the activity of the epithelial cells ceasing.

This is not entirely true, for the appearance of the papillomatous growths already described is coincident with the onset of this atrophic condition, but they are localised conditions, and do not affect the general statement.

Yet a later stage is found when the underlying corium has become converted into granulation tissue and caused loss of the epithelium or of the warts, if there were any, and resulted in the production of an ulcerated surface.

Changes in the Elastic Tissue.—The first change apparent in the elastic tissue is a diminution in the density of the subepithelial plexus; and while this change is going on in the superficial tissues, an increase in the density of the elastic tissue is taking place in the deeper parts of the corium, more particularly in connection with the various special structures met with in this position, as for instance the hair follicles, the sweat coils, and sebaceous glands. In no instance was there any evidence of an initial increase in the amount of the subepithelial plexus of elastic tissue.

With further exposure to the rays the disappearance of the elastic tissue becomes more complete, until ultimately a narrow zone of completely de-elasticised connective tissue is seen lying under the epidermis, while in the deeper structures the same narrow zone of tissue free from elastin is met with round the hair follicles, until they, at a later date, in their turn disappear, and an absolutely de-elasticised tissue results.

The Changes in the Epithelial Appendages are first manifest in the hair follicles, which appear at first to hypertrophy. They become larger, more cellular and irregular in shape. There is no evidence that any increase in the growth of the hair takes place, but the new hair which grows after defluvium has followed a moderate dose of rays is often thicker than the original hair, and sometimes exhibits a tendency to curl.

With continuous exposure to the rays the hypertrophy is followed by atrophy, the follicles lose all traces of the hairs, get gradually smaller, and recede from the surface, so that the appearance of isolated clumps of epithelial cells lying in the connective tissues is produced. The cells in these epithelial clumps lose their staining reactions, degenerate into irregular structureless masses, and ultimately disappear altogether.

Similar changes occur in the sebaceous glands, which disappear *pari passu* with the hair follicles.

The mode in which these changes are brought about will be considered later.

The Connective Tissues.—The main mass of the connective tissue of the corium undergoes a hyaline change, with the result that it looks more dense than usual and stains badly.

This applies to the major part of the connective tissue, but round the hair follicles and sebaceous glands there is a zone of much more cellular and more active-looking tissue which stains well and shows no sign of degeneration.

It would appear possible that it is upon the activity of this sheath of connective tissue surrounding the follicles that their atrophy and disappearance depend.

At a later stage the connective tissue undergoes further change, and is ultimately converted into a granulation tissue, such as was described as occurring in Cases I and II of the carcinoma series.

No giant-cell formation has been observed, and there is very little increase in wandering cells. Plasma cells are not present in any number as in the case of inflammatory conditions of ordinary character, and were only met with in X-ray dermatitis when the condition was such that malignant change appeared imminent.

The Nerves.—No microscopic evidence of changes in the nerves is brought forward, but we must suppose from the clinical evidence of the very profound alterations which are present in tactile sensibility, that some change is induced in the nerves to which this must be attributed. Whether this change is in the nature of a primary degeneration or is the result of strangulation of the nerves by new-formed connective tissue is not certain, but in view of the fact that this tactile change is an early symptom, it would appear probable that the former is the case. The acuity of tactile sense has been determined in several cases in which X-rays have been applied for the treatment of secondary nodules of cancer where the skin was not involved in growth, and it was found that there was considerable diminution.

Changes in the blood-vessels have been noted by many observers, the change being in the nature of an obliterative arteritis.

The effect of X-rays upon the blood vessels of an irradiated area is well illustrated by a case reported by Dunn,* in which sloughing of the flaps occurred after amputation of a breast which had been previously exposed to the rays. Very little

* Internat. Journ. of Surgery, Aug. 1903.

bleeding was noticed at the operation, and within 48 hours a slough had formed along the entire length of the wound.

Two similar cases are referred to, and suggest the possibility that the X-rays had so altered the nutrition of the parts that the blood supply of the flaps—which in ordinary cases is probably not far from a minimum—had become dangerously small.

A point of some interest is the limited extent to which the action of the rays penetrates; for in none of the cases of advanced dermatitis was there any affection of the palmar surface of the finger or hand. As one knows, it is unusual from the nature of the necessary manipulations for the palms to be exposed, and it is apparent therefore that although the thickness of tissue represented by a finger readily permits the passage of those rays producing photographic effects, yet it is opaque to the injurious rays. However, as already mentioned, in some of the cases there are certain changes in the bones which must be attributed either to a direct action of the rays on the bony tissue, or upon its nervous or vascular supply, and indicating a relatively great penetration of the injurious rays.

The protective action of a relatively thin layer of living tissue is shown in a striking manner by the results obtained on exposing the tails of rats to the rays for long periods. The rats were placed in small lead cages which completely protected their bodies, but allowed the projection of the tail from a small hole at the end, in such a manner that only the dorsal aspect of the tail was exposed to the direct action of the rays. This method was devised now over a year ago,* as it was found that if the whole rat were exposed, death occurred before any marked superficial changes showed themselves.

It was found that when the tail was exposed for a long period in this manner, marked dermatitis ensued, the whole circumference being affected at the tip where movement in all directions was possible; but nearer the base of the tail, where the dorsal surface was the only part exposed, the changes were well-defined and confined to this surface.

* The experiments upon which the accompanying observations are based were carried out by Dr. Lazarus-Barlow.

The accompanying illustration shows a drawing of a transverse section of such a tail, in which three zones will be apparent—

(1) The dorsal surface, where there is advanced dermatitis with disappearance of the surface epithelium and the epithelial appendages; (2) a ventral zone where there is no departure from the normal; and (3) on either side an intermediate zone, where the rays would reach the surface tangentially, and in which the irregularity and hypertrophy

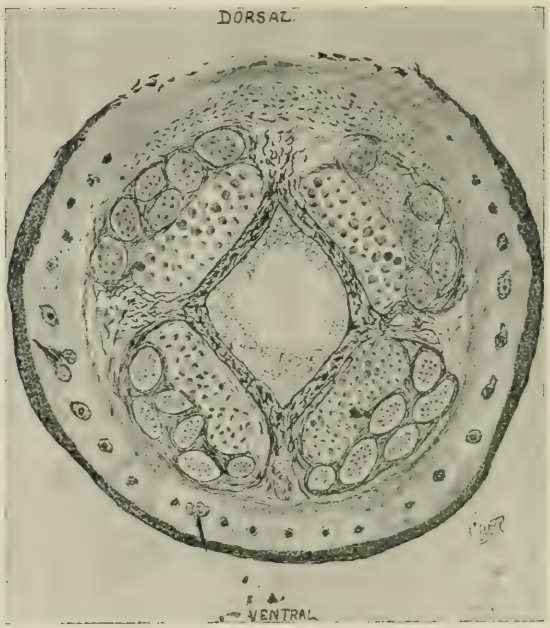
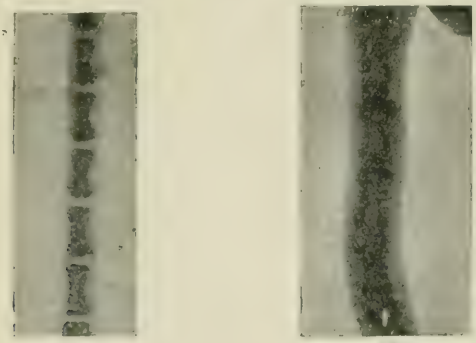


FIG. 2.—Drawing of a transverse section of a Rat's tail after prolonged exposure of its dorsal surface to X-rays. Note the normal hair bulbs—each surrounded by a small amount of fat—on the ventral surface, the disappearance of the surface epithelium, the hair bulbs and sebaceous glands, and the formation of granulation tissue on dorsal surface. The intermediate zones show thickening and slight irregularity of surface epithelium and hypertrophy of hair follicles.

of the epithelium of the skin, the hair bulbs and the sebaceous glands illustrate the stimulating action of a limited dosage of the rays.

Changes in the Bones.—As already mentioned, in some of the cases of X-ray dermatitis the bones show a considerable degree of alteration, as shown by the very much lighter shadow they give in a skiagram.

What the precise nature of this change is it has not as yet been possible to determine, but all degrees of the change are met with, from slight rarefaction to complete disappearance. It was the absolute and entire disappearance of the bone in the first case of carcinoma described in this paper that attracted attention to the bones, and subsequent investigation showed that in other cases the same changes obtain to a less degree; indicating that the loss of bone in the above case was probably not entirely due to the invasion of bone by the



(*a*) (*b*)

FIG. 3.—Skiagrams of Rats' tails: (*a*) NORMAL: (*b*) AFTER EXPOSURE TO X-RAYS until the production of severe dermatitis. The skiagrams were taken side by side on the same plate at the same time: although the bone of the irradiated tail is thicker than that of the unexposed, the shadow cast by the latter is denser. These points show more clearly on the original plate than in the reproduction.

new growth. Only one other case has thus far been met with in which the disappearance was anything like so complete, and in this case, although no malignant growth has occurred the terminal phalanx has been removed for intractable suppurative onychia; and a skiagram of the stump shows complete disappearance of the bone of the second phalanx. This case is all the more interesting in that a series of skiagrams has been taken and the gradual absorption of the bone is apparent. The manner in which the bone has disappeared is

of interest, for the change does not appear to have affected the whole bone, but certain parts only, so that the earlier skiagrams show areas which appear to have been cleanly punched out from the edge of the phalanx.

In the experiments carried out with rats a slight degree of this bony change was induced, as is shown in the accompanying skiagrams of an irradiated tail side by side with a normal tail. The greater density of the shadow in the latter tail will be apparent. No minute changes could be recognised on histological examination.

INFLUENCE OF X-RAYS ON MALIGNANT GROWTHS.

The effects produced on the minute structure of malignant growths after treatment with X-rays are not as yet fully settled; the difficulty of getting material under satisfactory conditions, the absence of a "control," and the great variations which, it is probable, take place in the microscopic appearances of the same growth at different periods of its history, render the whole question one of considerable doubt and difficulty.

Dalous and Lasserre (Ann. de Derm. et Syph., April 1905, p. 304) described the changes occurring in an epithelioma and the skin surrounding it after nine exposures to the rays. They found changes which were most marked in the basal layers of cells and in the underlying elastic tissue; and venture to the somewhat sweeping conclusion that it follows from this that X-rays may be expected to have more beneficial effect upon what they call baso-cellular carcinoma—arising in basal cells—than on the carcinomata arising from the superficial layers of the epithelium.

In view of the uncertainty as to whether squamous cell carcinomata can arise in any other than the basal cells, this statement must be accepted with caution, although it is an undoubted fact that rodent cancer—the ultimate origin of which is probably closely associated with some of the more highly differentiated basal cells, i.e. possibly the cells of the hair follicles—is more benefited than squamous cell carcinomata of ordinary characters.

It is probable, however, that the superficial character of rodent cancer is an adequate explanation of the ease with which it is influenced.

In connection with the results obtained in certain cases of carcinoma, both of squamous and spheroidal type, it is of importance to consider upon what changes the beneficial results which often ensue depend. From what has gone before it will be gathered that some of the results, such as the relief of pain, will be probably due either to partial or complete degeneration of the sensory nerves. The cleaning up, &c., of ulcerated surfaces can be sufficiently explained by the chemical changes which have been shown to occur by Foulerton and Kellas.* But, more important than this, there are undoubtedly many cases in which either a primary malignant growth, such as a squamous cell carcinoma, or a rodent cancer, or subcutaneous nodules secondary to mammary carcinoma, have diminished in size, and even disappeared. This improvement may obviously depend upon one of two factors, either a primary degeneration of the cancer cell as a result of the rays, and its destruction by phagocytic action, or else gradual destruction of the cell by the surrounding connective tissue.

Of the first we have at present no definite evidence; many specimens of irradiated cancer have been reported upon, but the reports are too conflicting, too vague, too unconvincing to be accepted as showing changes specifically due to the X-rays, especially when it is remembered that none of these recorded changes is of a special or peculiar nature, or different from those met with from time to time under ordinary circumstances.

On the other hand we have definite evidence of very special activity of the connective tissues, the tendency of which appears to be the inclusion and destruction of any epithelial elements present, as is well shown by the findings in the various microscopic sections described. It is probably on these grounds that the shrinkage and ultimate disappearance of an irradiated new growth may be explained, and in this connection it is of interest to recall the well-known fact of the great difficulties met with in obtaining the complete healing of a lupoid or rodent ulcer which has invaded cartilage, where this connective tissue activity obviously cannot occur.

* Proc. Roy. Soc., B. Vol. 78, 1906.

The Influence of X-rays upon Lupus.—As already mentioned, it appears certain that since cases of lupus have been treated by X-rays the number of instances in which a malignant process has supervened has very materially increased. It is extremely difficult to substantiate a statement like this with definite figures, for cancer supervening on lupus was by no means uncommon before X-rays were discovered. However, it is the opinion of all who have been in the habit of dealing with cases of this character that such is the case. Since we know not the causes of the formation of a carcinoma in a lupoid ulcer in which X-rays have not been used, it would be idle to speculate as to the exact causation of the carcinoma, or rather of the greater frequency of carcinoma, in those cases which have been X-rayed. It is interesting, however, to note that it is stated that it is in cases where the dose of the rays has been large enough to cause a burn that carcinoma has developed. Pernet* has published a note on the histology of X-rayed lupus, in which he states that after irradiation he noticed plasma cells in large numbers, disappearance of the elastic tissue, and collagenous change of the connective tissues of the corium. I have found similar appearances in two cases. These changes, however, can hardly have great significance, as they are such as are constantly met with in certain kinds of lupus, even when not X-rayed.

The difficulties of actually determining the changes which take place in an irradiated area of lupus are considerable, owing to the fact that many of the changes which occur in irradiated skin are such as are constantly met with in lupus, or, indeed, any chronic inflammatory condition.

In connection with the question of the nature of the radiations which produce these changes, it is interesting to compare with the results of X-rays those induced by prolonged exposure to the emanations of the salts of radium. Continued exposure is followed at first by slight reddening of the skin; the redness fades in a few days, but a faint blush persists. At the end of a week or so the redness becomes more intense, and the skin presents the appearance of an erythema papule, being slightly swollen and œdematous. In ten days vesicu-

* Lancet. Sept. 6, 1902.

lation occurs, and in a fortnight there is a definite ulcer, which is tender and painful on pressure.

These ulcers take some time to heal, and result in a white depressed scar with a pigmented areola; the pigmentation being ultimately replaced by a well-marked band of telangiectases surrounding, but not encroaching upon, the scar.

In certain cases in which radium burns have been experimentally induced, these changes have been quite constant, and the resulting scars have all had the same characters.

The question of protection from the injurious effects of the rays is intimately connected with the problem as to which property of the rays it is that produces these effects.

Thomson * has shown that an acute burn may be produced in animals, and that lupus may be satisfactorily treated in human beings, even when the irradiated area is screened off by means of a sheet of aluminium; and yet we know that in the case of X-ray workers the skin of the lower forearms—which must be almost as much exposed as the backs of the hands—is never affected above the level to which the lower end of the coat or shirt sleeve extends.

Aluminium permits the passage of the rays, but cuts off the discharge from the electric field around the tube; it is obvious, therefore, that the cathodal discharge is the potent factor in producing burns. And it therefore seems probable that the material of a coat or shirt sleeve has the power of cutting off certain rays which are able to pass through an aluminium sheet.

Advantage has been taken of this fact in the treatment of cases at the Middlesex Hospital, the exposed area being now always covered with a linen sheet with the object of avoiding burns.

In addition to the various factors introduced by varying amount of current, distance of irradiated area from anode, and the hardness of tube, it is undoubtedly true that individual idiosyncrasy is of importance. Thus a worker, at present in this laboratory, in October 1902 exposed an area one inch in diameter on the forearm for ten minutes at a distance of 4½ inches from the cathode. Two months later an ulcer

* Brit. Journ. of Dermatol. Oct. 1903.

appeared which healed in about three weeks, but has left a depressed, hairless, pigmented cicatrix with numerous telangiectatic capillaries. A colleague who underwent a similar exposure immediately afterwards with the same tube showed no changes in the skin either early or late. Schmidt* describes a case in which for the purpose of skiagraphy a hand was exposed to X-rays for half an hour. Two or three weeks after exposure the skin became red, and later developed a bluish tint. Atrophic changes supervened, and the skin ultimately became in a condition which was compared to wrinkled cigarette paper, and was still in this condition five years afterwards.

This is also interesting as showing the lasting effects which may occasionally follow a single long exposure, which usually results in a change of a more acute character.

The question of protection from the influence of the rays is one of considerable importance, and the methods in general use may be divided into two groups :—

(1) Those in which the rays are screened close to their point of origin in such a manner as to allow none but the part which it is desired to expose to be affected.

(2) Those in which parts of the patient which it is not desired to irradiate, and parts of the operator which come within the sphere of action of the rays, are screened off by means of screens of various shapes and kinds, such for instance as leaden plates applied to the patient, and protective gloves and aprons, &c., worn by the operator.

The latest method is the use of a box lined either with lead, or with indiarubber impregnated with lead, in which all necessary switches are arranged, and in which the operator stands.

But all the various means of protection are ineffective unless care is taken that the current is always shut off when any alteration in the position of the tube, &c., is made.

The conclusions that I would draw from a consideration of the above facts are :—

1°. That the application of X-rays to healthy tissues in moderate doses—what may be regarded as a moderate dose probably varying considerably with the idiosyncrasy of the

* Archiv. f. Dermat. u. Syph. Jan. 1903, lxiv.

individual—results in stimulation of normal physiological processes, i.e. the growth of epithelial and other cell elements, hairs, &c.

2°. That a single large dose may result in an acute change somewhat resembling an ordinary burn or other form of destructive dermatitis.

3°. Administration of doses for a long period ultimately results in complete atrophy of the epithelial elements and degenerative changes in the connective tissues.

4°. That the conditions contained in (1) and (3) ultimately result in a state which disposes to the occurrence of carcinoma. Whether the formation of epithelial new growth is simply due to the chronic irritation abundantly present in these cases, or whether the X-rays by their action exert some special influence, it is at present impossible to say.

A SIMPLE APPARATUS FOR DRAWING FROM THE MICROSCOPE.

By CECIL W. ROWNTREE.

The apparatus described below was devised in order to overcome the difficulties and uncertainties of drawing with the camera lucida.

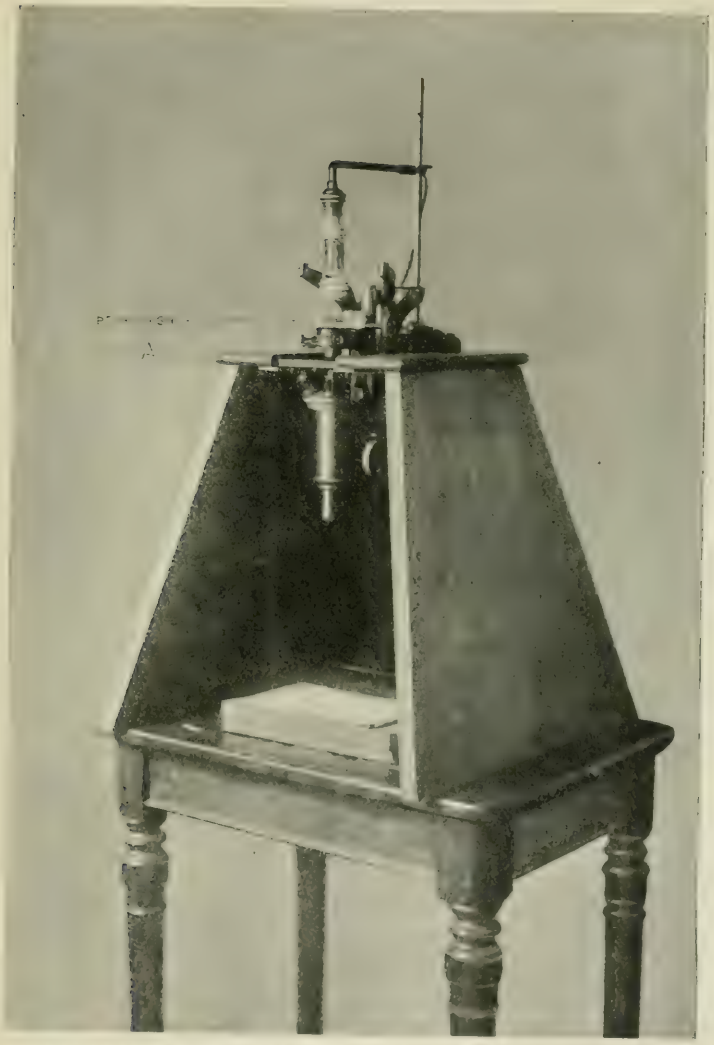
It is essentially a projection apparatus, in which an image of the object to be examined is obtained by inverting an ordinary microscope, the magnified image being caught upon a sheet of white paper at any distance directly below the eye-piece.

Reference to the accompanying photograph of the apparatus will illustrate how this is done.

The microscope, from which the mirror should be detached, rests upon a wooden support A, which is about twelve inches square, and in which is cut a slot, the edges of which are armed with brass slats upon which the microscope stage —which must be quite plain—accurately fits.

Three sides of the apparatus are boxed in to exclude light, and in order to increase stability these sides should be made fairly solid, and should slope outwards so that the lower edge of the box measures twenty inches square.

The light for the microscope requires to be powerful; that used in this laboratory is a Nernst lamp of 200 volts with a straight filament. The lamp should be fixed quite rigidly, with the filament about one and a half inches above the condenser of the microscope, and the illumination may be considerably enhanced by removing the globe and using the naked filament. But if this be done a petri dish filled with a saturated alum solution should rest upon the condenser in order to protect the microscope from the heat generated by the lamp; and the eyes should be protected by enclosing the lamp in a metal cylinder—a tobacco tin with the bottom removed answers admirably.



APPARATUS FOR DRAWING FROM THE MICROSCOPE.

Drawings are obtained by placing the microscopic section in position on what is now the upper surface of the stage of the microscope, and on focussing it will be found that the image may be caught directly below the eye-piece at any distance desired.

Definition of the image of course diminishes as the distance increases, but if the box be made about eighteen inches high it will be found that there is plenty of room for drawing, and that definition is still excellent.

Either pen, pencil, or brush may be utilised, or if desired water-colour may be used, as it is obviously an easy matter to get a close approximation to the colours of the image.

The magnification of the image varies directly with the objective, the oculars, and the distance between the ocular and the drawing-paper, so that one has a wide range of choice. The best results are obtained by using a low-power objective, and increasing the ocular or the distance; but with a good lamp and good lenses it is quite possible in a darkened room to get excellent illumination and definition with a $\frac{1}{12}$ oil immersion objective. When using oil immersion lenses it is well to choose one with a close working distance in order to avoid trouble with the oil due to the inverted position of the microscope.

If a plane mirror be arranged just below the eye-piece it is possible to project an image in any desired direction; with favourable conditions and a low objective good definition may be obtained up to twelve feet, so that the apparatus is of considerable service for the purpose of demonstrating microscopic objects to small classes.

The whole apparatus may be made by any intelligent carpenter for a few shillings.

EYRE AND SPOTTISWOODE, LTD., HIS MAJESTY'S PRINTERS, LONDON, N.E. [H.S.—7/18.]

RC
31
L8M5
v.13

Middlesex Hospital
Archives

GERSTS

Archives of The Middlesex Hospital.

THESE Archives are published with the object of recording work done in the Wards, Laboratories, and Special Departments of The Middlesex Hospital, and contain contributions upon subjects connected with—

1. Clinical Medicine and Surgery.
2. The Investigation of Cancer.
3. Research carried on in the Clinical and Pathological Laboratories.
4. The work of the Special Departments of the Hospital and School.

About three Volumes will appear during the year, as they become ready for publication.

The price of each Volume will necessarily vary with the cost of production, but in the belief that many past Students of the Hospital and others will desire to possess them, it has been decided to accept a nominal subscription of Half-a-guinea per annum for the whole series.

Subscriptions may be sent to the Secretary-Superintendent of The Middlesex Hospital.

THE LAST NUMBER, VOLUME XII., CONTAINS :—